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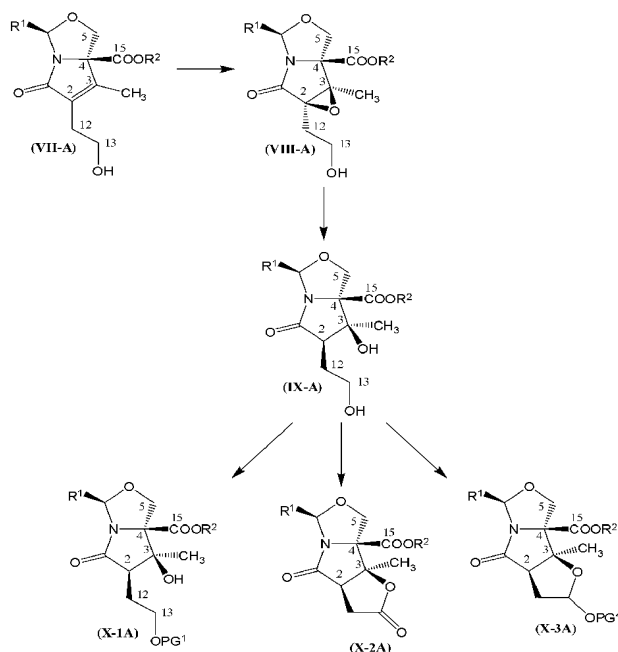
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[Continued on next page]

(54) Title: TOTAL SYNTHESIS OF SALINOSPORAMIDE A AND ANALOGS THEREOF

Figure 4a



(57) Abstract: The present application relates to certain compounds and to methods for the preparation of certain compounds that can be used in the fields of chemistry and medicine. Specifically, described herein are methods for the preparation of various compounds and intermediates, and the compounds and intermediates themselves. More specifically, described herein are methods for synthesizing Salinosporamide A and its analogs that includes forming a compound of formula (VIII).

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TOTAL SYNTHESIS OF SALINOSPORAMIDE A AND ANALOGS THEREOF**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Patent Application Nos. 61/034,900, entitled "Total Synthesis of Salinosporamide A and Analogs Thereof," filed March 7, 2008; and 61/073,545, entitled "Total Synthesis of Salinosporamide A and Analogs Thereof," filed June 18, 2008, both of which are incorporated herein by reference in their entirety, including any drawings.

BACKGROUNDField

[0002] The present application discloses certain compounds and methods for the preparation of certain compounds that can be used in the fields of chemistry and medicine.

Description

[0003] Cancer is a leading cause of death in the United States. Despite significant efforts to find new approaches for treating cancer, the primary treatment options remain surgery, chemotherapy and radiation therapy, either alone or in combination. Surgery and radiation therapy, however, are generally useful only for fairly defined types of cancer, and are of limited use for treating patients with disseminated disease. Chemotherapy is the method that is generally useful in treating patients with metastatic cancer or diffuse cancers such as leukemias. Although chemotherapy can provide a therapeutic benefit, it often fails to result in cure of the disease due to the patient's cancer cells becoming resistant to the chemotherapeutic agent. Due, in part, to the likelihood of cancer cells becoming resistant to a chemotherapeutic agent, such agents are commonly used in combination to treat patients.

[0004] Similarly, infectious diseases caused, for example, by bacteria, fungi and protozoa are becoming increasingly difficult to treat and cure. For example, more and more bacteria, fungi and protozoa are developing resistance to current antibiotics and

chemotherapeutic agents. Examples of such microbes include *Bacillus*, *Leishmania*, *Plasmodium* and *Trypanosoma*.

[0005] Furthermore, a growing number of diseases and medical conditions are classified as inflammatory diseases. Such diseases include conditions such as asthma to cardiovascular diseases. These diseases continue to affect larger and larger numbers of people worldwide despite new therapies and medical advances.

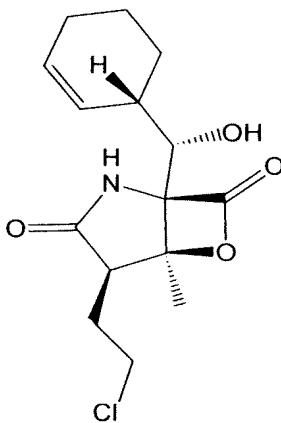
[0006] Therefore, a need exists for additional chemotherapeutics, anti-microbial agents, and anti-inflammatory agents to treat cancer, inflammatory diseases and infectious disease. A continuing effort is being made by individual investigators, academia and companies to identify new, potentially useful chemotherapeutic and anti-microbial agents.

[0007] Marine-derived natural products are a rich source of potential new anti-cancer agents and anti-microbial agents. The oceans are massively complex and house a diverse assemblage of microbes that occur in environments of extreme variations in pressure, salinity, and temperature. Marine microorganisms have therefore developed unique metabolic and physiological capabilities that not only ensure survival in extreme and varied habitats, but also offer the potential to produce metabolites that would not be observed from terrestrial microorganisms (Okami, Y. 1993 *J Mar Biotechnol* 1:59). Representative structural classes of such metabolites include terpenes, peptides, polyketides, and compounds with mixed biosynthetic origins. Many of these molecules have demonstrable anti-tumor, anti-bacterial, anti-fungal, anti-inflammatory or immunosuppressive activities (Bull, A.T. *et al.* 2000 *Microbiol Mol Biol Rev* 64:573; Cragg, G.M. & D.J. Newman 2002 *Trends Pharmacol Sci* 23:404; Kerr, R.G. & S.S. Kerr 1999 *Exp Opin Ther Patents* 9:1207; Moore, B.S 1999 *Nat Prod Rep* 16:653; Faulkner, D.J. 2001 *Nat Prod Rep* 18:1; Mayer, A. M. & V.K. Lehmann 2001 *Anticancer Res* 21:2489), validating the utility of this source for isolating invaluable therapeutic agents. Further, the isolation of novel anti-cancer and anti-microbial agents that represent alternative mechanistic classes to those currently on the market will help to address resistance concerns, including any mechanism-based resistance that may have been engineered into pathogens for bioterrorism purposes.

SUMMARY

[0008] The embodiments disclosed herein generally relate to the total synthesis of chemical compounds, including heterocyclic compounds and analogs thereof. Some embodiments are directed to the desired chemical compound and intermediate compounds. Other embodiments are directed to the individual methods of synthesizing the chemical compound and intermediate compounds.

[0009] An embodiment disclosed herein relates to a method for synthesizing Salinosporamide A and analogs thereof, wherein Salinosporamide A has the following structure:



[0010] One embodiment described herein relates to a method of synthesizing a compound of formula (IX) from compounds of formulae (VII) and (VIII), in which the compound of formula (IX) can be used to synthesize Salinosporamide A and its analogs.

[0011] Another embodiment described herein relates to a method of synthesizing a compound of formula (XV) from compounds of formulae (IX), (X-1), (XI-1), (XII-1), (XIII-1) and (XIV-1), in which the compound of formula (XV) can be used to synthesize Salinosporamide A and its analogs.

[0012] Still another embodiment described herein relates to a method of synthesizing a compound of formula (XV) from compounds of formulae (IX), (X-2), (XI-2), (XII-2), (XIII-2), (XIV-2) and (XVII), in which the compound of formula (XV) can be used to synthesize Salinosporamide A and its analogs.

[0013] Yet still another embodiment described herein relates to a method of synthesizing a compound of formula (XV) from compounds of formulae (IX), (X-3), (XI-

3), (XII-3), (XIII-3), (XIV-3) and (XVII), in which the compound of formula (XV) can be used to synthesize Salinosporamide A and its analogs.

[0014] One embodiment described herein relates to a method of synthesizing a compound of formula (VII) from compounds of formulae (I), (II), (III-1), (IV), (V) and (VI), in which the compound of formula (VII) can be used to synthesize Salinosporamide A and its analogs.

[0015] Another embodiment described herein relates to a method of synthesizing a compound of formula (VI) from diketene and compounds of formulae (I), (III-2) and (V), in which the compound of formula (VI) can be used to synthesize a compound of formula (VII) along with Salinosporamide A and its analogs. In some embodiments, a compound of formula (VI) can be synthesized from diketene and compounds of formulae (I) and (III-2). In an embodiment, a compound of formula (VI) can be obtained from diketene and compounds of formulae (I) and (III-2) without isolation of any intermediate compounds that are formed during the reaction.

[0016] Still another embodiment described herein relates to a method of synthesizing a compound of formula (VI) from acetoacetic acid and compounds of formulae (I), (III-2) and (V), in which the compound of formula (VI) can be used to synthesize a compound of formula (VII), Salinosporamide A and analogs of Salinosporamide A. In other embodiments, a compound of formula (VI) can be synthesized from acetoacetic acid and compounds formulae (I) and (III-2). In an embodiment, a compound of formula (VI) can be obtained from acetoacetic acid and compounds of formulae (I) and (III-2) without isolation of any intermediate compounds that are formed during the reaction.

[0017] Yet still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (III-2). Still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (VII). Yet still another embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (VIII). One embodiment described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (IX).

[0018] Some embodiments described herein relates to a method for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (XXII). In some embodiments, a compound of formula (XXII) can be used to obtain a compound of formula (VII), in which the compound of formula (VII) can be used to synthesize Salinosporamide A and its analogs.

[0019] Other embodiments described herein relates to a method for synthesizing analogs for Salinosporamide A through one or more of the following compounds of formulae (XXII), (XXIV), (XXV), (XXVI), (XXVII), (XXVIII), (XXIX), (XXX) and (XXXI). In some embodiments, analogs of Salinosporamide A can be obtained through a compound of formula (XXII). In an embodiment, analogs of Salinosporamide A can have the structure of a compound of formula (XXXI-A-1). In another embodiment, analogs of Salinosporamide A can have the structure of a compound of formula (XXXV).

[0020] Still other embodiments described herein relates to a method of synthesizing a compound of formula (XXV) from compounds of formulae (XXII) and (XXIV), in which the compound of formula (XXIV) can be used to synthesize Salinosporamide A and its analogs.

[0021] An embodiment described herein relates to a method of synthesizing a compound of formula (VIII) from a compound of formula (VII). Other embodiments described herein relate to a method synthesizing a compound of formula (IX) from a compound of formula (VIII). Some embodiments described herein relate to a method of synthesizing a compound of formula (VI), for example a compound of formula (VI-A), from a compound of formula (V) such as a compound of formula (Va-A). Other embodiments described herein relate to a method of obtaining a compound of formula (VII) from a compound of formula (VI). Still other embodiments described herein relate to a method of synthesizing a compound of formula (X-2) from a compound of formula (IX). An embodiment described herein relates to a method of synthesizing a compound of formula (XXIV) from a compound of formula (XXII). Other embodiments described herein relate to a method synthesizing a compound of formula (XXV) from a compound of formula (XXIV).

[0022] One embodiment described herein relates to a compound of formula (Va-A). Another embodiment described herein relates to a compound of formula (VI-A). Still another embodiment described herein relates to a compound of formula (VII). Yet still another embodiment described herein relates to a compound of formula (VIII). Still another embodiment described herein relates to a compound of formula (IX). An embodiment described herein relates to a compound of formula (XXII). Another embodiment described herein relates to a compound of formula (XXIV). Still another embodiment described herein relates to a compound of formula (XXV).

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Figure 1 illustrates retrosynthetic schemes for synthesizing a compound of formula (VII).

[0024] Figure 2 illustrates retrosynthetic schemes for synthesizing compound of formulae (XIV-1A), (XIV-2A) and (XIV-3A).

[0025] Figure 3 illustrates retrosynthetic schemes for synthesizing Salinosporamide A and analogs thereof.

[0026] Figures 4 and 4a-e illustrates methods of synthesizing Salinosporamide A and analogs thereof starting with a compound of formula (I) and a compound of formula (II), a compound of formula (I) and acetoacetic acid or a compound of formula (I) and diketene..

[0027] Figure 5 illustrates a method of synthesizing a compound of formula (I) from (S)-serine.

[0028] Figure 6 shows the chemical structure of Salinosporamide A.

[0029] Figure 7 shows a ^1H NMR spectrum of a compound of formula (I-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0030] Figure 8 shows a ^1H NMR spectrum of the ester precursor to a compound of formula (II) in CDCl_3 .

[0031] Figure 9 shows a ^1H NMR spectrum of the protected ester precursor of a compound of formula (II) in CDCl_3 .

[0032] Figure 10 shows a ^1H NMR spectrum of a compound of formula (II) in CDCl_3 .

[0033] Figure 11a shows a ^1H NMR spectrum of a compound of formula (III-1B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0034] Figure 11b shows a LC-MS of a compound of formula (III-1B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$).

[0035] Figure 12a shows a ^1H NMR spectrum of a compound of formula (IV-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0036] Figure 12b shows a NOESY spectrum of a compound of formula (IV-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0037] Figure 12c shows a ^1H NMR spectrum of a compound of formula (IV-B1) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0038] Figure 12d shows a ^1H NMR spectrum of a compound of formula (IV-B2) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0039] Figure 12e shows a LC-MS of a compound of formula (IV-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$).

[0040] Figure 13 shows a ^1H NMR of a compound (VI-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0041] Figure 14 shows a ^{13}C NMR spectrum of a compound (VI-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0042] Figure 15 shows a ^1H NMR spectrum of a compound (VII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0043] Figure 16 shows a ^{13}C NMR spectrum of a compound (VII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0044] Figure 17 shows a ^1H NMR spectrum of a compound (VIII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0045] Figure 18 shows a ^{13}C NMR spectrum of a compound (VIII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0046] Figure 19 shows a NOESY spectrum of a compound (VIII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0047] Figure 20 shows a ^1H NMR spectrum of a compound (X-1B with $\text{PG}^1 = \text{Bz}$, $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0048] Figure 21 shows a ^{13}C NMR spectrum of a compound (X-1B with $\text{PG}^1=\text{Bz}$, $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0049] Figure 22 shows a NOESY spectrum of a compound of formula (X-1B with $\text{PG}^1=\text{Bz}$, $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0050] Figure 23 shows a ^1H NMR spectrum of a compound (XI-1B) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0051] Figure 24 shows a ^{13}C NMR spectrum of a compound (XI-1B) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0052] Figure 25 shows a ^1H NMR spectrum of a compound (X-2B) ($\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0053] Figure 26 shows a ^{13}C NMR spectrum of a compound (X-2B) ($\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0054] Figure 27 shows an ORTEP representation of the X-ray crystal structure of compound (X-2B) ($\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0055] Figure 28 shows a ^1H NMR spectrum of a compound of formula (I-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0056] Figure 29 shows a ^{13}C NMR spectrum of a compound of formula (I-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0057] Figure 30 shows a ^1H NMR spectrum of a compound (III-1A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0058] Figure 31 shows a ^{13}C NMR spectrum of a compound (III-1A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0059] Figure 32 shows a ^1H NMR spectrum of a compound (IV-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0060] Figure 33 shows a ^{13}C NMR spectrum of a compound (IV-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0061] Figure 34 shows a ^1H NMR spectrum of a compound (VI-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0062] Figure 35 shows a ^{13}C NMR spectrum of a compound (VI-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0063] Figure 36 shows a ^1H NMR spectrum of a compound (VII-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0064] Figure 37 shows a ^{13}C NMR spectrum of a compound (VII-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0065] Figure 38 shows a ^1H NMR spectrum of a compound (VIII-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0066] Figure 39 shows a ^{13}C NMR spectrum of a compound (VIII-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0067] Figure 40 shows a ^1H NMR spectrum of a compound (X-1A) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0068] Figure 41 shows a ^{13}C NMR spectrum of a compound (X-1A) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0069] Figure 42 shows a ^1H NMR spectrum of a compound (XI-1A) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0070] Figure 43 shows a ^{13}C NMR spectrum of a compound (XI-1A) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0071] Figure 44 shows a ^1H NMR spectrum of a compound (X-2A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0072] Figure 45 shows a ^{13}C NMR spectrum of a compound (X-2A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0073] Figure 46 shows a ^1H NMR spectrum of a compound (XI-2A) ($\text{R}^2 = \text{methyl}$) in DMSO-d_6 and CDCl_3 mixture.

[0074] Figure 47 shows a ^{13}C NMR spectrum of a compound (XI-2A) ($\text{R}^2 = \text{methyl}$) in DMSO-d_6 and CDCl_3 mixture

[0075] Figure 48 shows a ^1H NMR spectrum of a compound (XI-2A) ($\text{R}^2 = \text{methyl}$ and C-5-O-TES) in CDCl_3 .

[0076] Figure 49 shows a ^1H NMR spectrum of a compound (XII-2A) ($\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0077] Figure 50 shows a ^{13}C NMR spectrum of a compound (XII-2A) ($\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0078] Figure 51 shows a ^1H NMR spectrum of a compound (III-2A) ($\text{R}^1 = t$ -butyl and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0079] Figure 52 shows a ^1H NMR spectrum of a compound (Va-A) ($\text{R}^1 = t$ -butyl and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

[0080] Figure 53 shows a ^{13}C NMR spectrum of a compound (Va-A) ($\text{R}^1 = t$ -butyl and $\text{R}^2 = \text{methyl}$) in CDCl_3 .

DETAILED DESCRIPTION

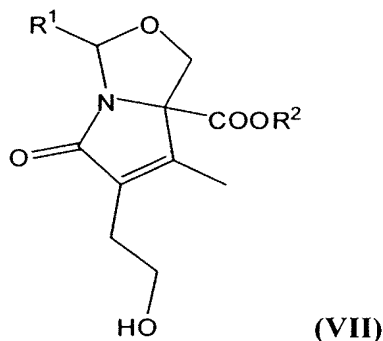
[0081] Numerous references are cited herein. The references cited herein, including the U.S. patents cited herein, are each to be considered incorporated by reference in their entirety into the present specification, unless otherwise noted.

[0082] Embodiments include, but are not limited to, methods for the preparation of various compounds and intermediates, and the compounds and intermediates themselves. In some embodiments, one or more substituents, one or more compounds, or groups of compounds can be specifically excluded in any one or more of the methods or compounds as described more fully below.

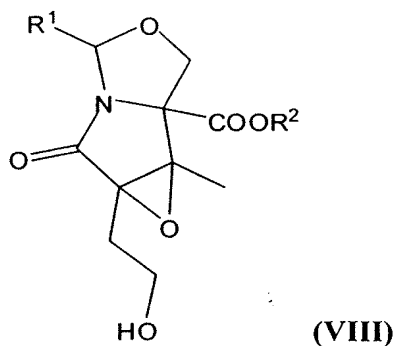
[0083] Described herein are methods for synthesizing Salinosporamide A, and analogs thereof. Salinosporamide A and several analogs, as well as methods of making the same are described in U.S. Provisional Patent Applications Nos., 60/480,270, filed June 20, 2003; 60/566,952, filed April 30, 2004; 60/627,461, filed November 12, 2004; 60/633,379, filed December 3, 2004; 60/643,922, filed January 13, 2005; 60/658,884, filed March 4, 2005; 60/676,533, filed April 29, 2005; 60/567,336, filed April 30, 2004; 60/580,838, filed June 18, 2004; 60/591,190, filed July 26, 2004; 60/627,462, filed November 12, 2004; 60/644,132, filed January 13, 2005; 60/659,385, filed March 4, 2005; 60/790,168, filed April 6, 2006; 60/816,968, filed June 27, 2006; 60/836,166, filed August 7, 2006; 60/844,132, filed September 12, 2006; and 60/855,379, filed January 17, 2007; U.S. Patent Applications Nos., 10/871,368, filed June 18, 2004; 12/136,688, filed June 1, 2008; 11/118,260, now U.S. Patent No. 7,276,530, filed April 29, 2005; 11/865,704, filed October 1, 2007; 11/412,476, filed April 27, 2006; 11/453,374, filed June 15, 2006; and 11/697,689, filed April 6, 2007; and International Patent Applications Nos., PCT/US2004/019543, filed June 18, 2004; PCT/US2005/044091, filed December

2, 2005, PCT/US2005/01484, filed April 29, 2005, PCT/US2006/016104, filed April 27, 2006; and PCT/US2007/008562, filed April 6, 2007; each of which is hereby incorporated by reference in its entirety.

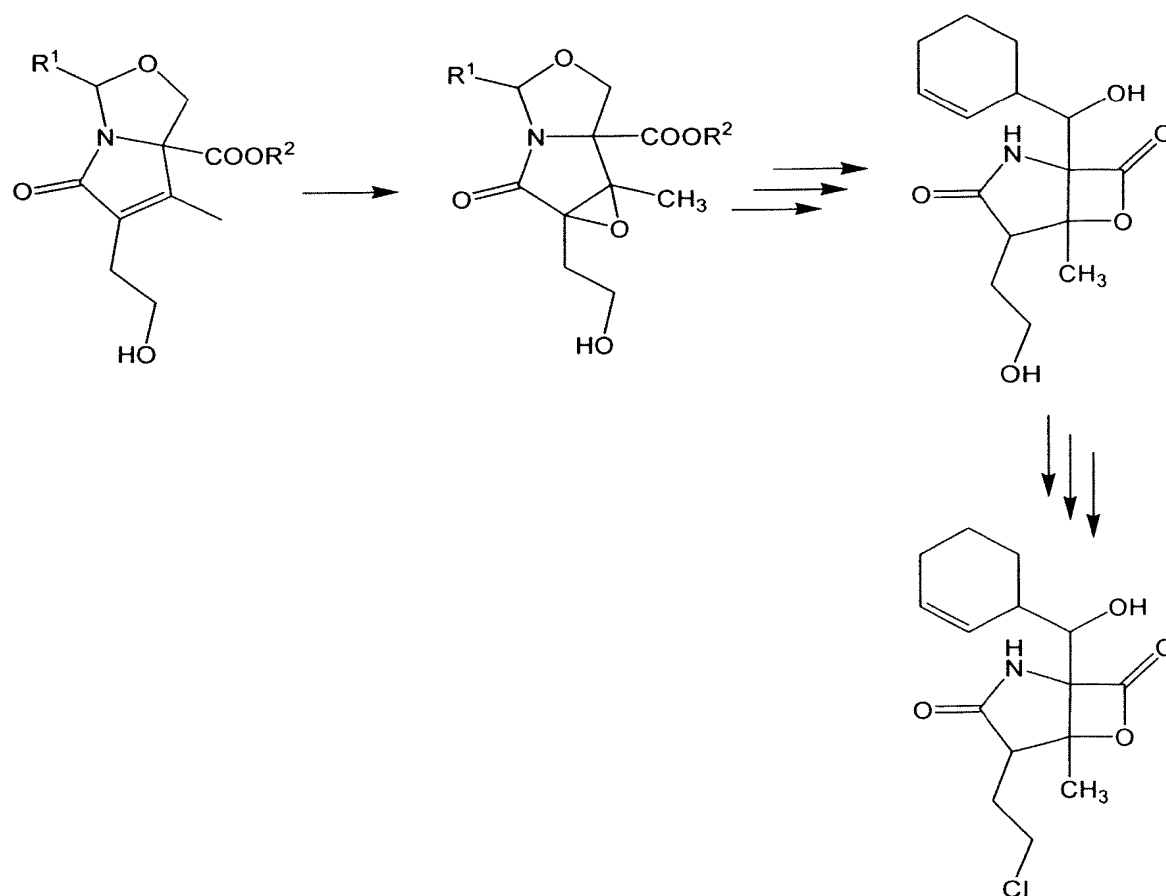
[0084] Provided herein are methods for synthesizing Salinosporamide A and its analogs through an intermediate compound of formula (VII):



[0085] As shown in Figure 4, the compound of formula (VII) can be synthesized from readily available starting materials, as described herein. The compound of Formula (VII) may be subsequently converted to Salinosporamide A or analogs thereof. For example Salinosporamide A or analogs thereof may be synthesized according to Scheme A. A retrosynthetic scheme providing additional details regarding synthesizing Salinosporamide A is shown in Figures 1-3. In an embodiment, Salinosporamide A and its analogs can be obtained through an intermediate compound, a compound of formula (VIII):



Scheme A



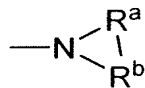
[0086] For the compounds described herein, each stereogenic carbon can be of R or S configuration. Although the specific compounds exemplified in this application can be depicted in a particular configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned unless otherwise specified. When chiral centers are found in the derivatives of the compounds, it is to be understood that the compounds encompasses all possible stereoisomers unless otherwise indicated.

[0087] The term “substituted” has its ordinary meaning, as found in numerous contemporary patents from the related art. See, for example, U.S. Patent Nos. 6,509,331; 6,506,787; 6,500,825; 5,922,683; 5,886,210; 5,874,443; and 6,350,759; all of which are incorporated herein in their entireties by reference. Examples of suitable substituents include but are not limited to alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy,

amino, alkyl amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxy, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-H, -SO₂-OH, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl and -SO₂-heteroaryl, heteroaryl, boronate alkyl, boronic acid, (OH)₂B-alkyl, phosphate and phosphate esters, phosphonooxy, phosphonooxyalkyl, azido, azidoalkyl, ammonium, carboxyalkyl, a salt of a carboxyalkyl, alkylamino, a salt of an alkylamino, dialkylamino, a salt of a dialkylamino, alkylthio, arylthio, carboxy, cyano, alkanesulfonyl, alkanesulfinyl, alkoxysulfinyl, thiocyno, boronic acidalkyl, boronic esteralkyl, sulfoalkyl, a salt of a sulfoalkyl, alkoxysulfonylalkyl, sulfooxyalkyl, a salt of a sulfooxyalkyl, alkoxysulfonyloxyalkyl, phosphonooxyalkyl, a salt of a phosphonooxyalkyl, (alkylphosphooxy)alkyl, phosphorylalkyl, a salt of a phosphorylalkyl, (alkylphosphoryl)alkyl, pyridinylalkyl, a salt of a pyridinylalkyl, a salt of a heteroarylalkyl guanidino, a salt of a guanidino, and guanidinoalkyl. Each of the substituents can be further substituted. The other above-listed patents also provide standard definitions for the term "substituted" that are well-understood by those of skill in the art.

[0088] Whenever a group is described as "optionally substituted" the group may be unsubstituted or substituted with one or more substituents as described herein.

[0089] As used herein, any "R" group(s) such as, without limitation, R¹, R², R³, R⁴, R⁵ and R⁶ represent substituents that can be attached to the indicated atom. An R group may be substituted or unsubstituted. If two "R" groups are covalently bonded to the same atom or to adjacent atoms, then they may be "taken together" as defined herein to form a cycloalkyl, aryl, heteroaryl or heterocycle. For example, without limitation, if R_{1a} and R_{1b} of an NR_{1a}R_{1b} group are indicated to be "taken together," it means that they are covalently bonded to one another to form a ring:



[0090] The term "alkyl," as used herein, means any unbranched or branched, substituted or unsubstituted, saturated hydrocarbon, with C₁-C₂₄ preferred, and C₁-C₆

hydrocarbons being preferred, with methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl, and pentyl being most preferred.

[0091] The term “alkenyl,” as used herein, means any unbranched or branched, substituted or unsubstituted, unsaturated hydrocarbon containing one or more double bonds. Some examples of alkenyl groups include allyl, homo-allyl, vinyl, crotyl, butenyl, pentenyl, hexenyl, heptenyl and octenyl.

[0092] The term “alkynyl” as used herein, means any unbranched or branched, substituted or unsubstituted, unsaturated hydrocarbon with one or more triple bonds

[0093] The term “cycloalkyl” refers to any non-aromatic, substituted or unsubstituted, hydrocarbon ring, preferably having five to twelve atoms comprising the ring. Furthermore, in the present context, the term “cycloalkyl” comprises fused ring systems such that the definition covers bicyclic and tricyclic structures.

[0094] The term “cycloalkenyl” refers to any non-aromatic, substituted or unsubstituted, hydrocarbon ring that includes a double bond, preferably having five to twelve atoms comprising the ring. Furthermore, in the present context, the term “cycloalkenyl” comprises fused ring systems such that the definition covers bicyclic and tricyclic structures.

[0095] The term “cycloalkynyl” refers to any non-aromatic, substituted or unsubstituted, hydrocarbon ring that includes a triple bond, preferably having five to twelve atoms comprising the ring. Furthermore, in the present context, the term “cycloalkynyl” comprises fused ring systems such that the definition covers bicyclic and tricyclic structures.

[0096] The term “acyl” refers to hydrogen, lower alkyl, lower alkenyl, or aryl connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted or unsubstituted.

[0097] In the present context the term “aryl” is intended to mean a carbocyclic aromatic ring or ring system. Moreover, the term “aryl” includes fused ring systems wherein at least two aryl rings, or at least one aryl and at least one C₃₋₈-cycloalkyl share at least one chemical bond. Some examples of “aryl” rings include optionally substituted

phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl. An aryl group may be substituted or unsubstituted.

[0098] In the present context, the term “heteroaryl” is intended to mean a heterocyclic aromatic group where one or more carbon atoms in an aromatic ring have been replaced with one or more heteroatoms selected from the group comprising nitrogen, sulfur, phosphorous, and oxygen. Furthermore, in the present context, the term “heteroaryl” comprises fused ring systems wherein at least one aryl ring and at least one heteroaryl ring, at least two heteroaryl rings, at least one heteroaryl ring and at least one heterocyclyl ring, or at least one heteroaryl ring and at least one C₃₋₈-cycloalkyl ring share at least one chemical bond. A heteroaryl can be substituted or unsubstituted.

[0099] The terms “heterocycle” and “heterocyclyl” are intended to mean three-, four-, five-, six-, seven-, and eight-membered rings wherein carbon atoms together with from 1 to 3 heteroatoms constitute said ring. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that an aromatic π -electron system does not arise. The heteroatoms are independently selected from oxygen, sulfur, and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, and the like. Heterocyclyl rings may optionally also be fused to at least other heterocyclyl ring, at least one C₃₋₈-cycloalkyl ring, at least one C₃₋₈-cycloalkenyl ring and/or at least one C₃₋₈-cycloalkynyl ring such that the definition includes bicyclic and tricyclic structures. Examples of benzo-fused heterocyclyl groups include, but are not limited to, benzimidazolidinone, tetrahydroquinoline, and methylenedioxybenzene ring structures. Some examples of “heterocycles” include, but are not limited to, tetrahydrothiopyran, 4*H*-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2*H*-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyridine, pyridinium, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline,

oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane. A heterocycle group may be substituted or unsubstituted.

[0100] The term “alkoxy” refers to any unbranched, or branched, substituted or unsubstituted, saturated or unsaturated ether, with C₁-C₆ unbranched, saturated, unsubstituted ethers being preferred, with methoxy being preferred, and also with dimethyl, diethyl, methyl-isobutyl, and methyl-*tert*-butyl ethers also being preferred.

[0101] The term “cycloalkoxy” refers to any non-aromatic hydrocarbon ring comprising an oxygen heteroatom, preferably having five to twelve atoms comprising the ring. A cycloalkoxy can be substituted or unsubstituted.

[0102] The term “alkoxy carbonyl” refers to any linear, branched, cyclic, saturated, unsaturated, aliphatic or aromatic alkoxy attached to a carbonyl group. The examples include methoxycarbonyl group, ethoxycarbonyl group, propyloxycarbonyl group, isopropyloxycarbonyl group, butoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, cyclopentyloxycarbonyl group, cyclohexyloxycarbonyl group, benzyloxycarbonyl group, allyloxycarbonyl group, phenyloxycarbonyl group, pyridyloxycarbonyl group, and the like. An alkoxy carbonyl may be substituted or unsubstituted.

[0103] The term “(cycloalkyl)alkyl” is understood as a cycloalkyl group connected, as a substituent, via a lower alkylene. The (cycloalkyl)alkyl group and lower alkylene of a (cycloalkyl)alkyl group may be substituted or unsubstituted.

[0104] The terms “(heterocycle)alkyl” and “(heterocyclyl)alkyl” are understood as a heterocycle group connected, as a substituent, via a lower alkylene. The heterocycle group and the lower alkylene of a (heterocycle)alkyl group may be substituted or unsubstituted.

[0105] The term “arylalkyl” is intended to mean an aryl group connected, as a substituent, via a lower alkylene, each as defined herein. The aryl group and lower alkylene of an arylalkyl may be substituted or unsubstituted. Examples include benzyl, substituted benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl.

[0106] The term “heteroarylalkyl” is understood as heteroaryl groups connected, as substituents, via a lower alkylene, each as defined herein. The heteroaryl and lower alkylene of a heteroarylalkyl group may be substituted or unsubstituted.

Examples include 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, imidazolylalkyl, and their substituted as well as benzo-fused analogs.

[0107] The term “lower alkylene groups” are straight-chained tethering saturated hydrocarbon groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), and butylene ($-(\text{CH}_2)_4-$) groups. A lower alkylene group may be substituted or unsubstituted.

[0108] The term “halogen atom,” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, *i.e.*, fluorine, chlorine, bromine, or iodine, with bromine and chlorine being preferred.

[0109] As employed herein, the following terms have their accepted meaning in the chemical literature.

9-BBN	:9-borabicyclo[3.3.1]nonane
Bn	:benzyl
BnOH	:benzyl alcohol
BOC	: <i>tert</i> -butoxycarbonyl
BOPCl	:bis(2-oxo-3-oxazolidinyl)phosphinic chloride
t-BuOH	: <i>tert</i> -butanol/ <i>tert</i> -butyl alcohol
t-BuOK	:potassium <i>tert</i> -butoxide
Bz	:benzoyl
CAN	:ceric ammonium nitrate
DBN	:1,5-diazabicyclo[4.3.0]non-5-ene
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	:N,N-dicyclohexyl carbodiimide
DDQ	:2,3-dichloro-5,6-dicyanobenzoquinone
DIBALH	:diisobutylaluminum hydride
DMDO	:dimethyldioxirane
DMF	N,N-dimethylformamide
ESI	:electrospray ionization
EtOAc	:ethyl acetate

ID	:internal diameter
LC-MS	:liquid chromatography – mass spectrometry
LDA	:lithium diisopropylamide
LiAlH ₄	:lithium aluminum hydride.
mCPBA	: <i>meta</i> -chloroperoxybenzoic acid
MS	:mass spectrum
MsCl	:methanesulfonyl chloride
NaOMe	:sodium methoxide
NaOEt	:sodium ethoxide
NMO	:N-methylmorpholine N-oxide
NMR	:nuclear magnetic resonance
PCC	:pyridinium chlorochromate
Pd-C	:palladium on activated carbon
PDC	:pyridinium dichromate
PMB	: para-methoxybenzyl
PDC	:pyridinium dicromate
PPTS	:pyridinium p-toluene sulfonate
PTSA	:p-toluene sulfonic acid
RT	:room temperature
TES	:triethylsilyl
TFA	:trifluoroacetic acid
TFAA	:trifluoroacetic anhydride
TPAP	:tetrapropylammonium perruthenate
THF	:tetrahydrofuran
TLC	:thin layer chromatography

[0110] The terms “organometallic moiety” and “organometallic moieties” as used herein refer to any chemical compound that contains a metal-element bond(s) of a largely covalent character. The term “metal” as used herein include those elements traditionally classified as metals (e.g., lithium, magnesium, zinc, and tin) and those elements classified as metalloids (e.g., boron).

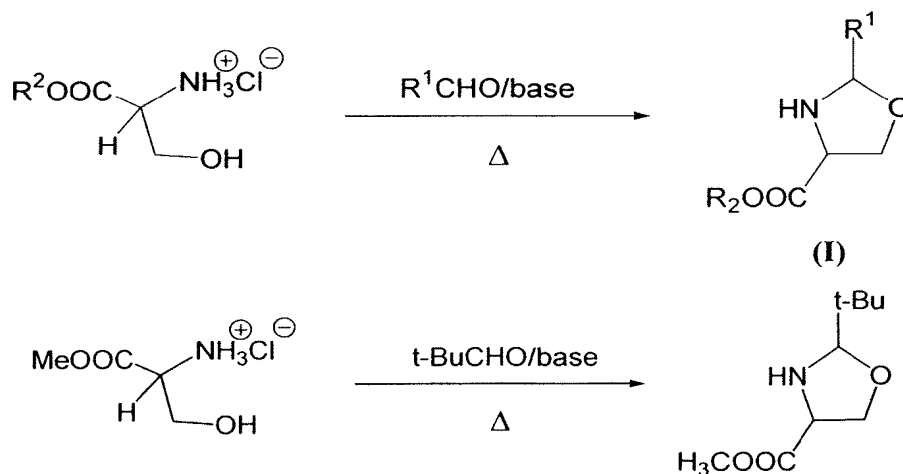
[0111] The terms “protecting group moiety” and “protecting group moieties” as used herein refer to any atom or group of atoms that is added to a molecule in order to prevent existing groups in the molecule from undergoing unwanted chemical reactions. Examples of protecting group moieties are described in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3. Ed. John Wiley & Sons, 1999, and in J.F.W. McOmie, *Protective Groups in Organic Chemistry* Plenum Press, 1973, both of which are hereby incorporated by reference. The protecting group moiety may be chosen in such a way, that they are stable to the reaction conditions applied and readily removed at a convenient stage using methodology known from the art. A non-limiting list of protecting groups include benzyl; substituted benzyl; unsubstituted or substituted alkylcarbonyls (e.g., t-butoxycarbonyl (BOC)); unsubstituted or substituted arylcarbonyls; unsubstituted or substituted arylalkylcarbonyls (e.g., benzyloxycarbonyl, benzoyl); unsubstituted or substituted alkoxy carbonyls; unsubstituted or substituted aryloxy carbonyls; substituted methyl ether (e.g. methoxymethyl ether); substituted ethyl ether; tetrahydropyranyl ether; silyl ethers (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, or t-butyldiphenylsilyl); esters (e.g. benzoate ester); carbonates (e.g. methoxymethylcarbonate); sulfonates (e.g. tosylate, mesylate); acyclic ketal (e.g. dimethyl acetal); cyclic ketals (e.g., 1,3-dioxane or 1,3-dioxolanes); acyclic acetal; cyclic acetal; acyclic hemiacetal; cyclic hemiacetal; and cyclic dithioketals (e.g., 1,3-dithiane or 1,3-dithiolane). As used herein, any "PG" group(s) such as, without limitation, PG¹, PG², PG⁴, PG⁵ and PG⁶ represent a protecting group moiety.

[0112] The terms “pure,” “purified,” “substantially purified,” and “isolated” as used herein refer to the compound of the embodiment being free of other, dissimilar compounds with which the compound, if found in its natural state, would be associated in its natural state. In some embodiments described as “pure,” “purified,” “substantially purified,” or “isolated” herein, the compound may comprise at least 50% or 75% of the mass, by weight, of a given sample. In other embodiments, the compound may comprise at least 90% or 95% of the mass, by weight, of a given sample. In still other embodiments, the compound may comprise at least 99% of the mass, by weight, of a given sample.

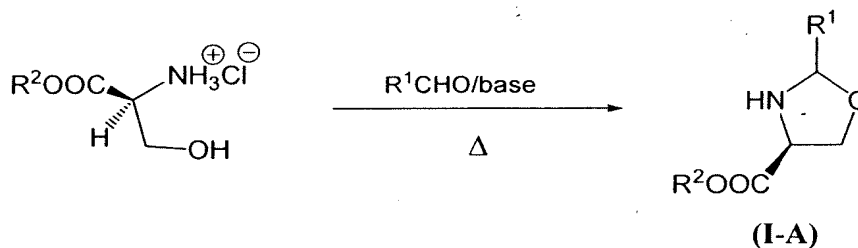
[0113] The terms “derivative,” “variant,” or other similar term refers to a compound that is an analog of the other compound.

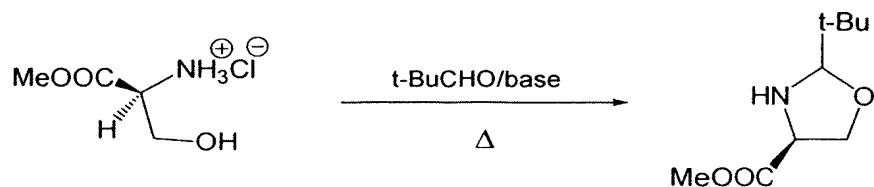
[0114] The starting compound of formula (I) may be synthesized from readily available materials. As shown in Scheme 1-1, a compound of formula (I) can be synthesized from a serine ester salt, an aldehyde and a base (e.g., triethylamine) at elevated temperatures. In some embodiments, the R^1 group can be hydrogen, unsubstituted or substituted C_{1-6} alkyl or unsubstituted or substituted aryl. In some embodiments, R_2 can be selected from hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, the serine ester salt can be a (L)-serine methylester salt which can form a compound of formula (I) with the stereochemistry shown in Scheme 1-2. In an embodiment, the aldehyde can be t-butyl aldehyde in which R^1 is t-butyl. In some embodiments, R^2 can be an unsubstituted or substituted C_{1-6} alkyl. In an embodiment, R^2 can be methyl.

Scheme 1-1



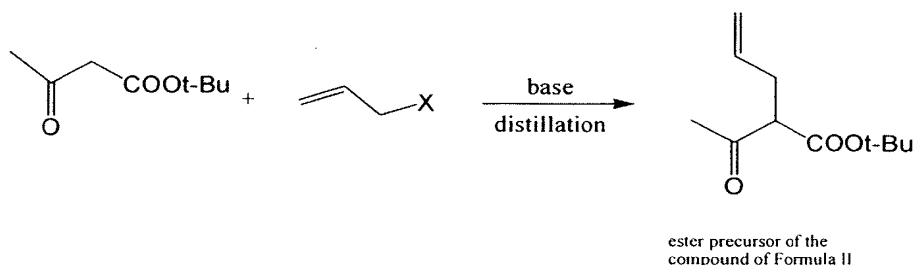
Scheme 1-2





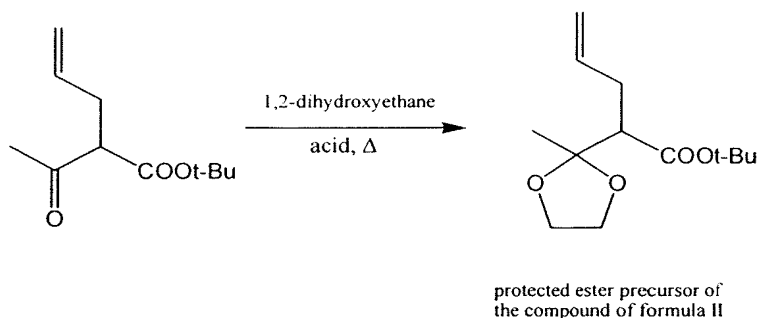
[0115] In some embodiments, a compound of formula (II) may be used as a starting material with a compound of formula (I). The compound of formula (II) can be synthesized according to Schemes 2, 3 and 4. The ester precursor of the compound of formula (II) can be prepared according to Scheme 2, starting with *tert*-butyl 3-oxobutanoate and a base (e.g., *t*-BuOK or NaH) and then adding an allyl halide.

Scheme 2



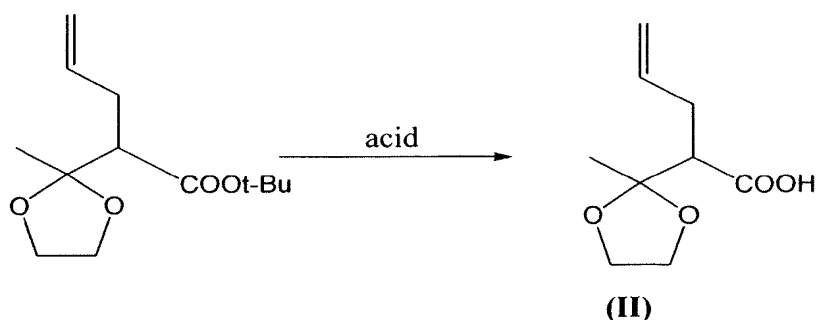
[0116] The acetal protected ester precursor of the compound of formula (II) can be prepared according to Scheme 3.

Scheme 3



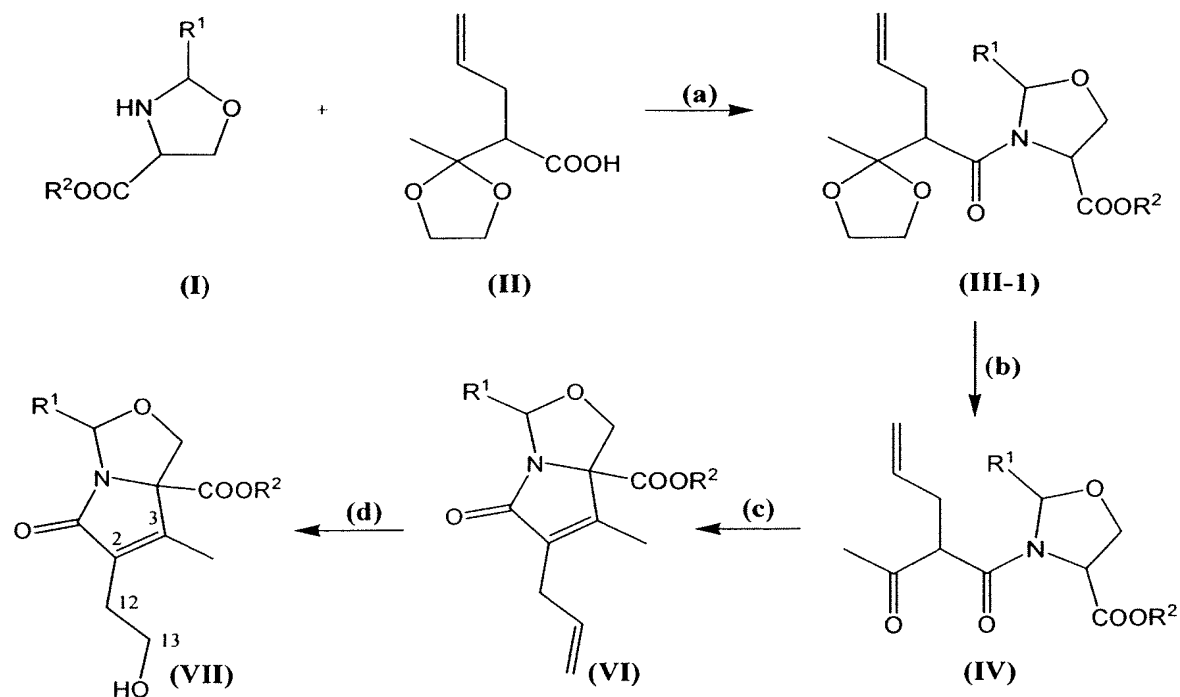
[0117] As shown in Scheme 4, the protected ester precursor of a compound of formula (II) can then be hydrolyzed to the carboxylic acid equivalent using an appropriate acid such as TFA or PTSA to form a compound of formula (II).

Scheme 4



[0118] A method of preparing a compound of formula (VII) from the starting compounds of formulae (I) and (II) is shown below in Scheme 5.

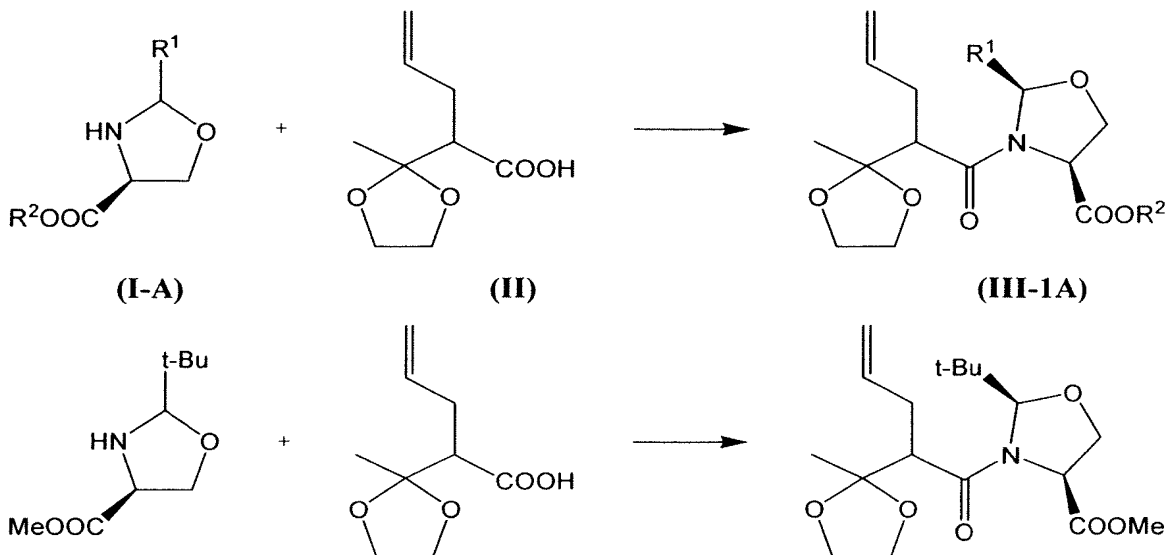
Scheme 5



[0119] In step (a) of Scheme 5, a compound of formula (III-1) can be formed by reacting a compound of formula (I) with a compound of formula (II) under suitable conditions. In some embodiments, the R¹ group can be hydrogen, unsubstituted or substituted C₁₋₆ alkyl or unsubstituted or substituted aryl. In an embodiment, the R¹ group can be t-butyl. In some embodiments, R² can be selected from hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, R² can be an unsubstituted

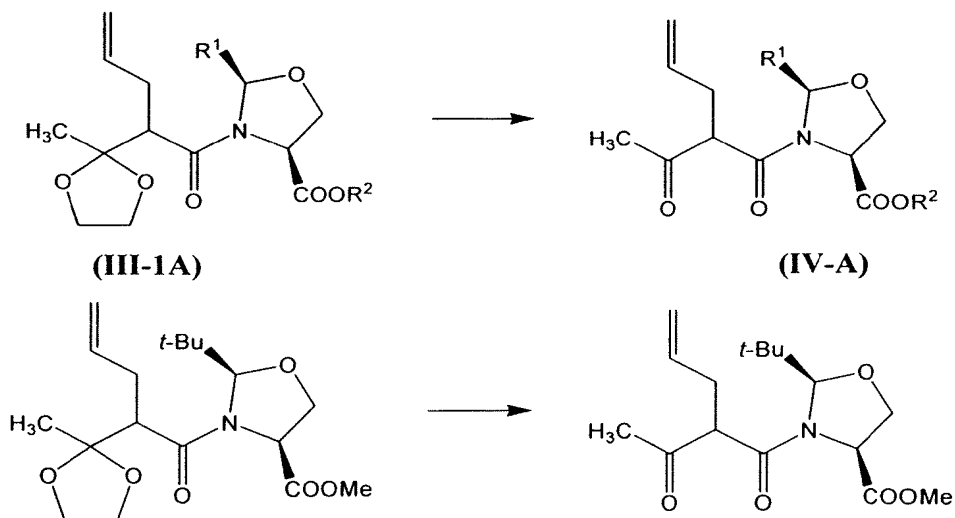
or substituted C_{1-6} alkyl. In an embodiment, R^2 can be methyl. For example, a compound of formula (I) can be added to a mixture containing a compound of formula (II), a mild base (e.g., triethylamine or N-methyl piperidine) and an acylating agent such as methanesulfonyl chloride, trifluoromethanesulfonyl chloride or chloromethylformate.

[0120] As examples, the compounds of formulae (I), (II) and (III-1) may have the following structures and stereochemistry:



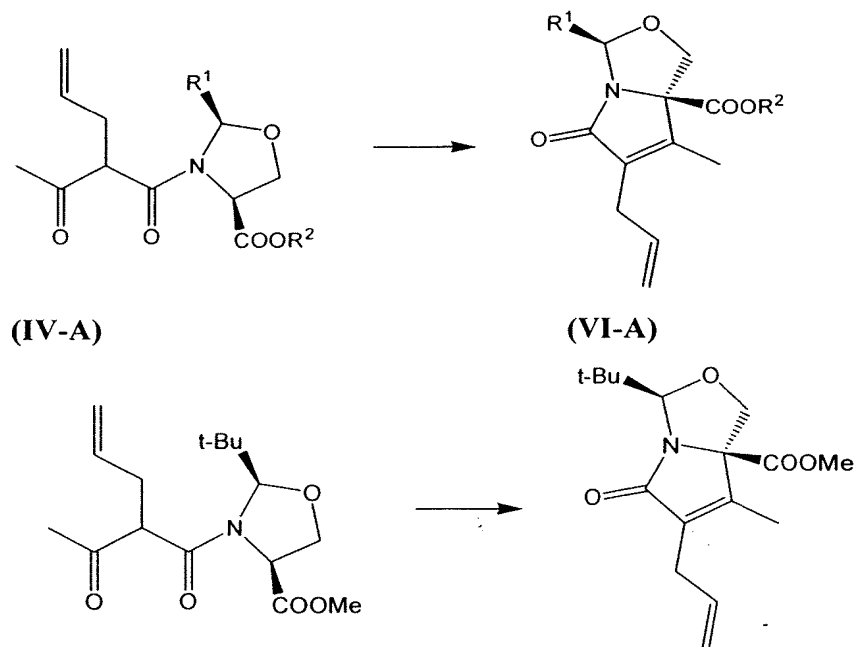
[0121] The compound of formula (III-1) can be deprotected to form a compound of formula (IV), as shown in step (b) of Scheme 5. One method for removing the acetyl protecting group includes reacting a compound of formula (III-1) with sodium iodide and a Lewis base such as cerium (III) chloride heptahydrate. A second method includes reacting a compound of formula (III-1) with iodine in acetone at an elevated temperature. Alternatively, a compound of formula (III-1) can be reacted with lithium tetrafluoroborate at an elevated temperature to form a compound of formula (IV).

[0122] Exemplary structures and stereochemistry of compounds of formulae (III-1) and (IV) are shown below:



[0123] As shown in step (c) of Scheme 5, treatment of a compound of formula (IV) with an appropriate base (e.g., *t*-BuOK, NaOMe, NaOEt or LDA) can induce an intramolecular aldol condensation reaction to form a compound of formula (VI).

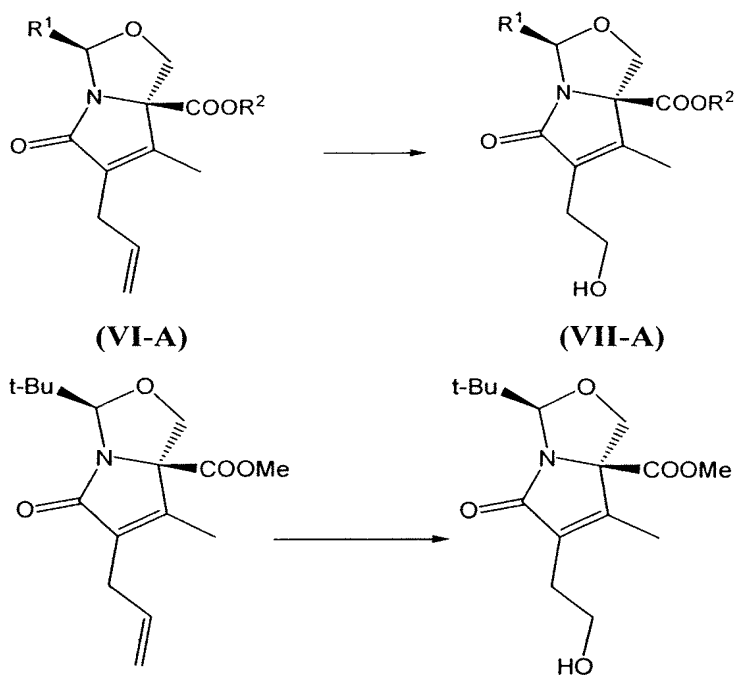
[0124] In an embodiment, the compounds of formulae (IV) and (VI) may have the following structures and stereochemistry:



[0125] In step (d) of Scheme 5, the terminal double bond of the allyl substituent at C-2 of the compound of formula (VI) can be converted to a primary hydroxyl group as shown by a compound of formula (VII). In some embodiments, the *R*¹

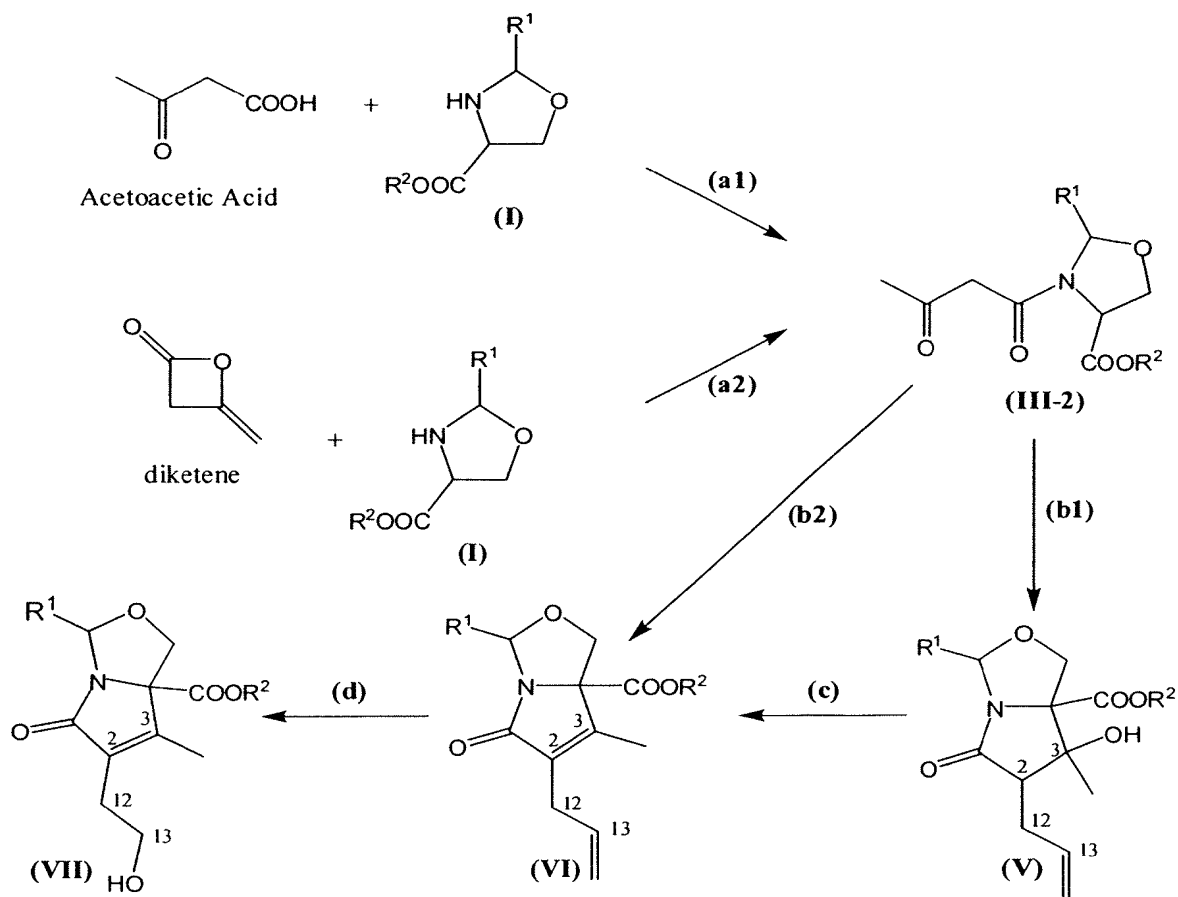
group can be hydrogen, unsubstituted or substituted C₁₋₆ alkyl or unsubstituted or substituted aryl. In an embodiment, the R¹ group can be t-butyl. In some embodiments, R² can be selected from hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, R² can be an unsubstituted or substituted C₁₋₆ alkyl. In an embodiment, R² can be methyl. Using methods known to those skilled in the art, the alkene may be oxidized to an aldehyde using an appropriate oxidizing agent (e.g., ozone, osmium tetroxide and sodium periodate). The resulting aldehyde can then be reduced to an alcohol to give a compound of formula (VII) using an appropriate reducing agent such as NaBH₄, LiAlH₄ or diisobutylaluminum hydride (DIBALH).

[0126] Examples the structures and stereochemistry of the compounds of formulae (VI) and (VII) are:



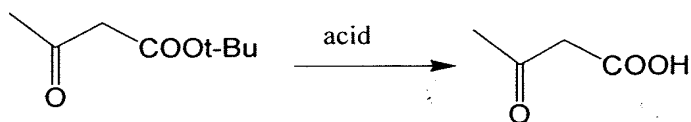
[0127] Alternatively, a compound of formula (VII) can be obtained by the methods shown below in Scheme 6.

Scheme 6



[0128] In some embodiments, acetoacetic acid may be used as a starting compound along with a compound of formula (I). Acetoacetic acid may be prepared as shown in Scheme 6a by hydrolyzing *tert*-butyl-3-oxobutanoate with an appropriate acid such as TFA, *p*-toluenesulphonic acid (PTSA) or HCl.

Scheme 6a

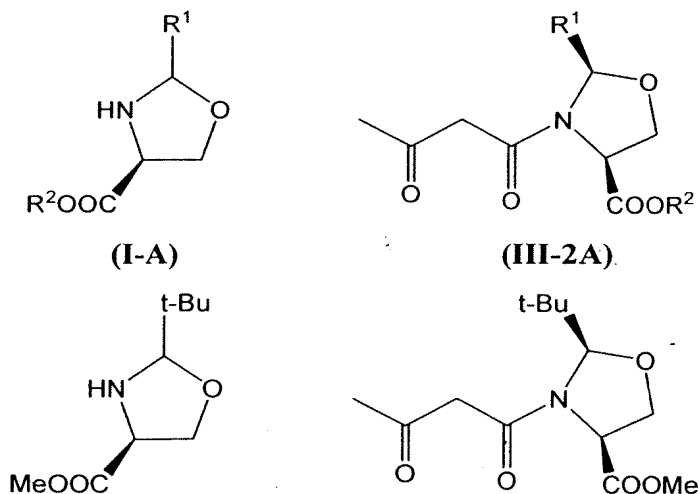


[0129] In step (a1) of Scheme 6, acetoacetic acid and a compound of formula (I) can be reacted together to form a compound of formula (III-2). In some embodiments, the R¹ group can be hydrogen, unsubstituted or substituted C₁₋₆ alkyl or unsubstituted or substituted aryl. In an embodiment, the R¹ group can be *t*-butyl. In some embodiments,

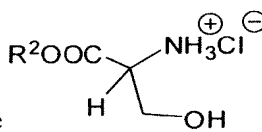
R^2 can be selected from hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, R^2 can be an unsubstituted or substituted C_{1-6} alkyl. In an embodiment, R^2 can be methyl. One method for forming a compound of formula (III-2) includes reacting a compound of formula (I) with acetoacetic acid and an appropriate coupling agent(s) such as dicyclohexylcarbodiimide, N,N' -diisopropylcarbodiimide, and/or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.

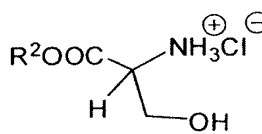
[0130] A compound of formula (III-2) can also be obtained starting with diketene and a compound of formula (I). As shown in step (a2) of Scheme 6, diketene and a compound of formula (I) can be added together to form a compound of formula (III-2). In some embodiments, the R^1 group can be hydrogen, unsubstituted or substituted C_{1-6} alkyl or unsubstituted or substituted aryl. In an embodiment, the R^1 group can be *t*-butyl. In some embodiments, R^2 can be selected from hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, R^2 can be an unsubstituted or substituted C_{1-6} alkyl. In an embodiment, R^2 can be methyl. The additional reaction of a compound of formulae (I) and diketene to form a β -keto amide can be facilitated through the use of a base. Suitable bases include, but are not limited to, amine bases (e.g., triethylamine) and pyridine.

[0131] In an embodiment, the compounds of formulae (I) and (III-2) can have the following structure and stereochemistry:

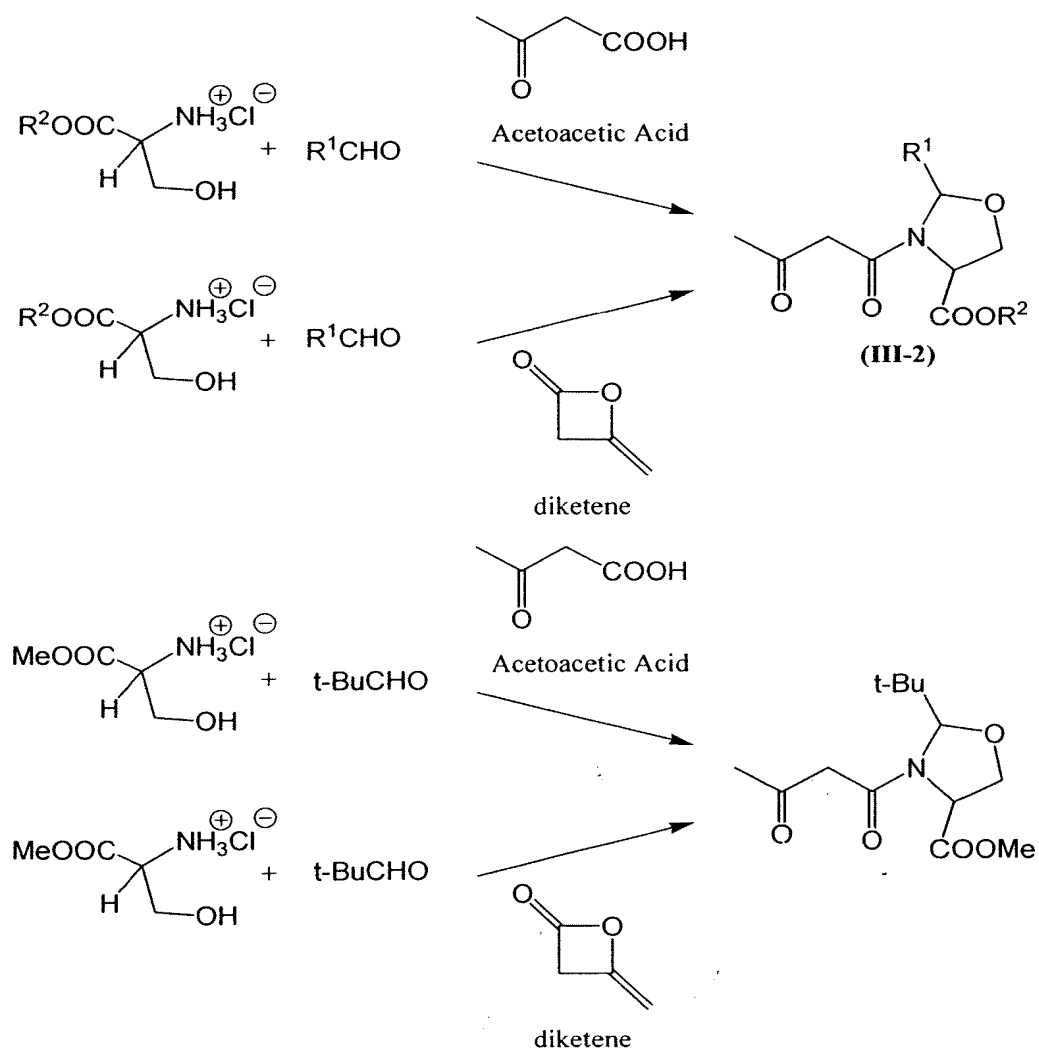


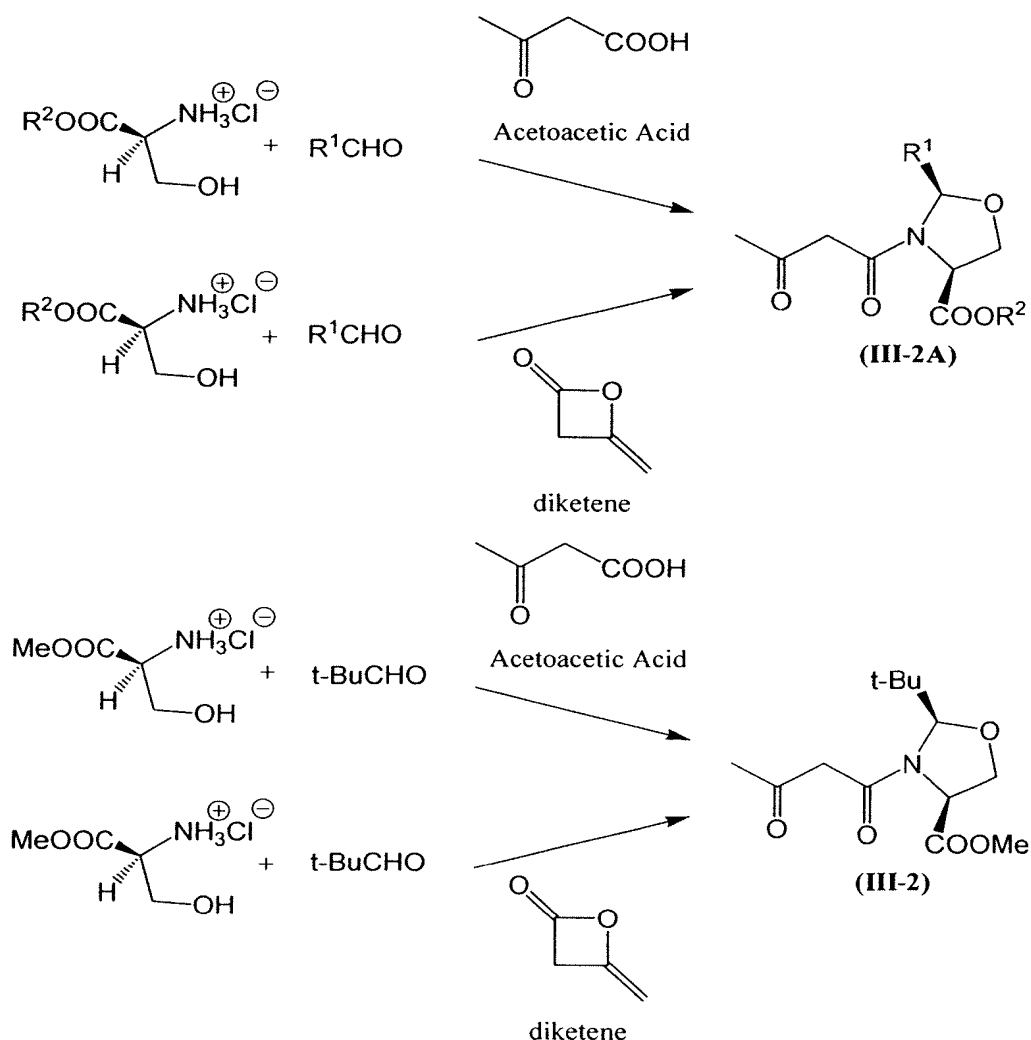
[0132] A compound of formula (III-2) can also be formed by combining together an aldehyde (for example, t-butylaldehyde), a compound having the

structure  and acetoacetic acid or diketene, without isolating any of the

intermediate compounds formed. In an embodiment,  can be a serine ester salt such as a (L)-serine methylester salt. To facilitate the reaction, an appropriate base can be used, for example, an amine base such as triethylamine or pyridine.

Scheme 7

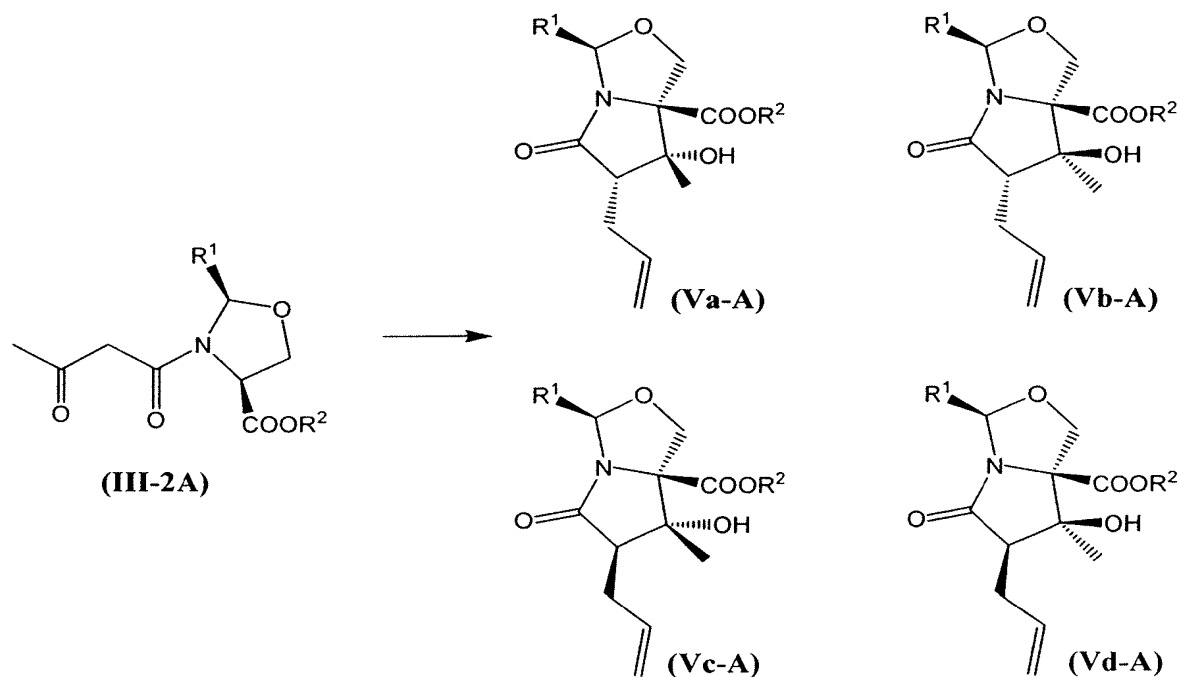


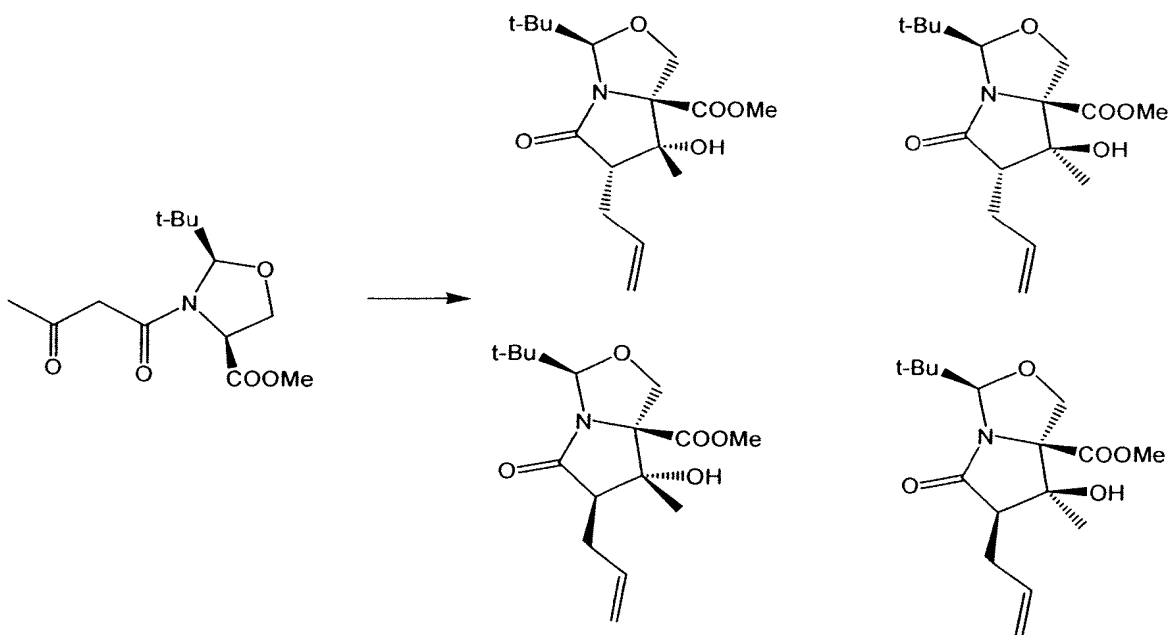


[0133] The compound of formula (III-2) can be converted to a compound of formula (V) through an intramolecular aldol reaction and alkylation, as shown in step (b1) of Scheme 6. The compound of formula (III-2) can be alkylated using methods known to those skilled in the art. For example, a compound of formula (III-2) can be reacted with an appropriate alkylating agent such as allyl bromide. The alkylated compound of formula (III-2) can then undergo an intramolecular aldol reaction to form the compound of formula (V). In some embodiments, the intramolecular aldol reaction can be induced using an appropriate base such as carbonate or bicarbonate base. Examples of suitable carbonate and bicarbonate bases include, but are not limited to, sodium carbonate, potassium carbonate, cerium(IV) carbonate and sodium bicarbonate.

In an embodiment, the base can be potassium carbonate. In an embodiment, the reaction can produce one or more diastereomers of a compound of formula (V), including a compound of formula (Va-A), a compound of formula (Vb-A), a compound of formula (Vc-A) and a compound of formula (Vd-A).

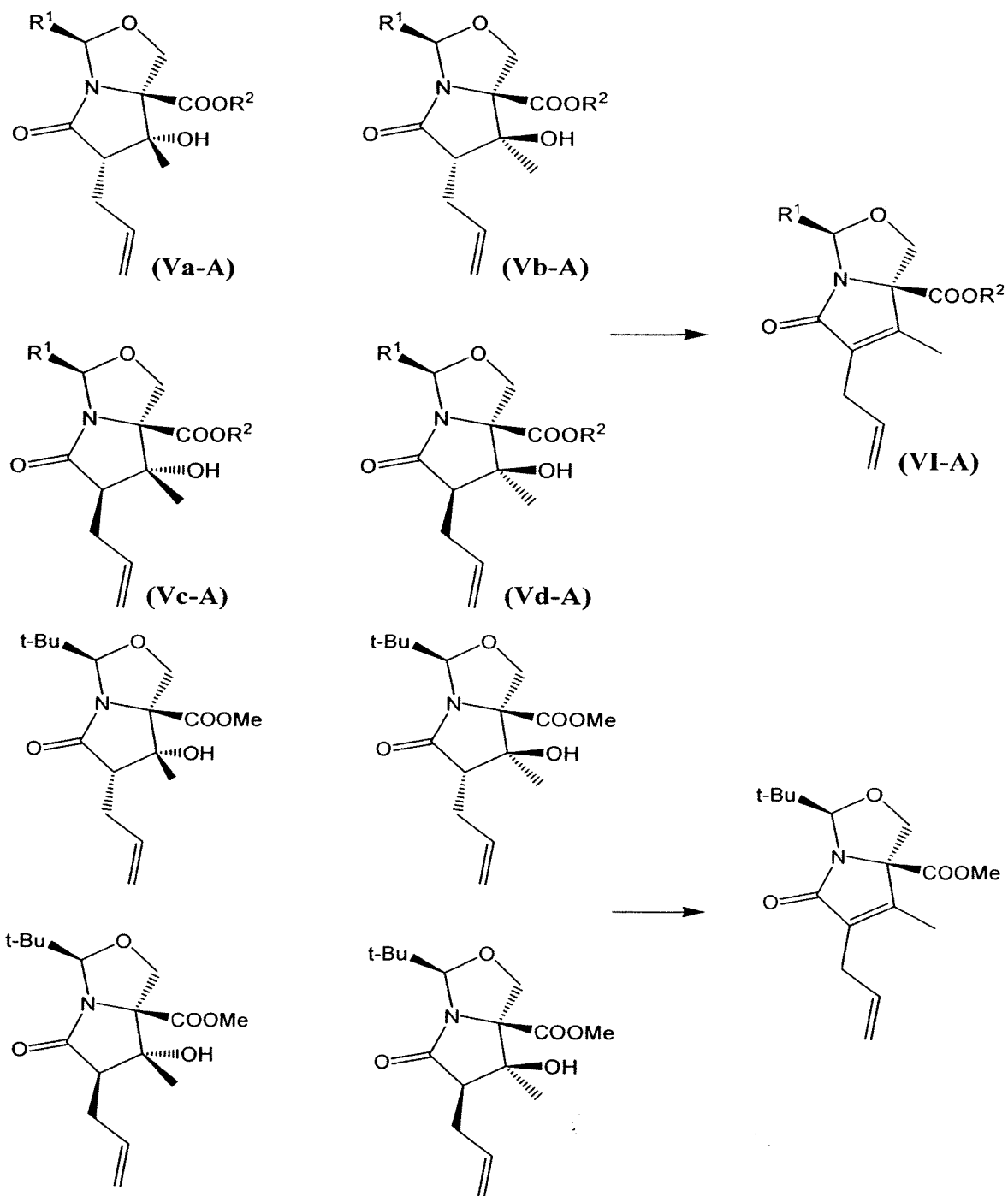
[0134] Exemplary structures and stereochemistry of compounds of formulae (III-2) and (V) are shown below:





[0135] The double bond between C-2 and C-3 can be obtained by dehydrating a compound of formula (V) to form a compound of formula (VI), as shown in step (c) of Scheme 6. A compound of formula (V) can be dehydrated, for example, by reacting the compound of formula (V) with an appropriate base, such as an amidine compound. Two examples of suitable amidine compounds include, but are not limited to, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). One or more of the aforementioned diastereomers of a compound of formula (V), such as a compound of formula (Va-A), a compound of formula (Vb-A), a compound of formula (Vc-A) and a compound of formula (Vd-A), can be used to obtain a compound of formula (VI).

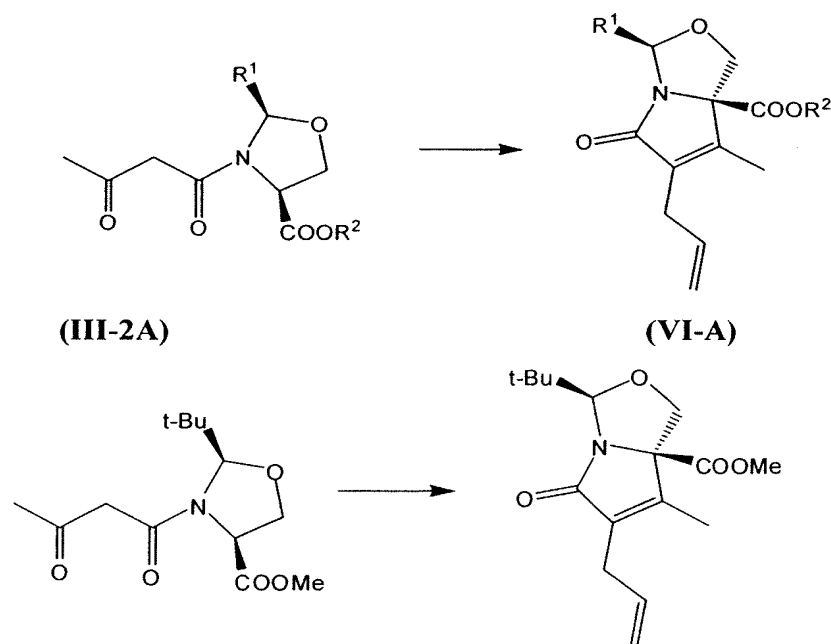
[0136] In an embodiment, the compounds of formulae (V) and (VI) can have the following structures and stereochemistry:



[0137] In another embodiment, a compound of formula (VI) can be obtained from a compound of formula (III-2), as shown in step (b2) of Scheme 6. In one reaction vessel, a compound of formula (III-2) can be alkylated, undergo an intramolecular aldol

condensation reaction in the presence of an appropriate base to obtain a compound of formula (VI). As described previously, allyl bromide (an alkylating reagent), and an amidine compound (base) can be used for obtaining a compound of formula (VI) from a compound of formula (III-2).

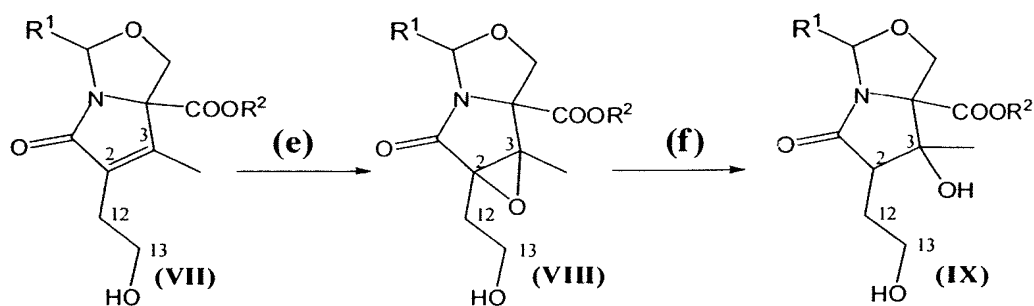
[0138] As examples, the compounds of formulae (III-2) and (VI) may have the following structures and stereochemistry:



[0139] As discussed previously, a compound of formula (VI) can be used to synthesize a compound of formula (VII) as described herein. For example, the alkene may be oxidized to an aldehyde using an appropriate oxidizing agent (e.g., ozone, osmium tetroxide and sodium periodate). The aldehyde can then be reduced to an alcohol to give a compound of formula (VII) using an appropriate reducing agent such as NaBH₄, LiAlH₄ or diisobutylaluminum hydride (DIBALH).

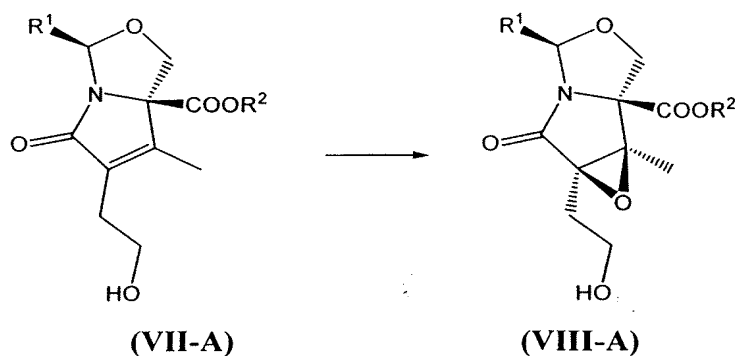
[0140] A compound of formula (IX) can be synthesized starting with a compound of formula (VII) is shown in Scheme 8. One example of this synthesis is shown in Figure 4a.

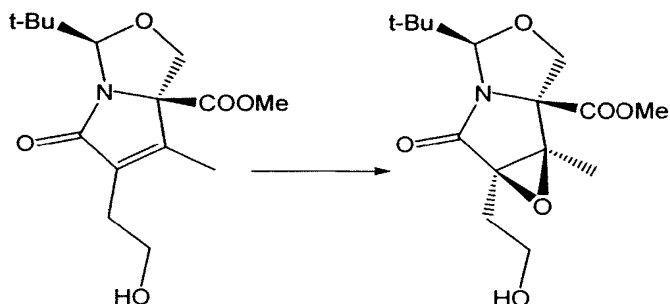
Scheme 8



[0141] A compound of formula (VII) can be oxidized to form a compound of formula (VIII) in which an epoxide is formed that includes C-2 and C-3. Various methods are known to those skilled in the art to form the epoxide. In some embodiments, formation of the epoxide can be stereospecific. In an embodiment, formation of the epoxide creates an (*R*)-stereocenter at C-2 and an (*R*)-stereocenter at C-3. By forming the epoxide stereospecifically, the desired stereochemistry present in Salinosporamide A and its analogs at C-2 and C-3 can be established upon cleavage of the epoxide. In an embodiment, the epoxide is formed using an appropriate peroxide such as *tert*-butyl hydroperoxide, *meta*-chloroperoxybenzoic acid (mCPBA) or dimethyldioxirane (DMDO). If needed, a base (e.g., benzyltrimethyl ammonium hydroxide) can also be employed to facilitate the epoxidation.

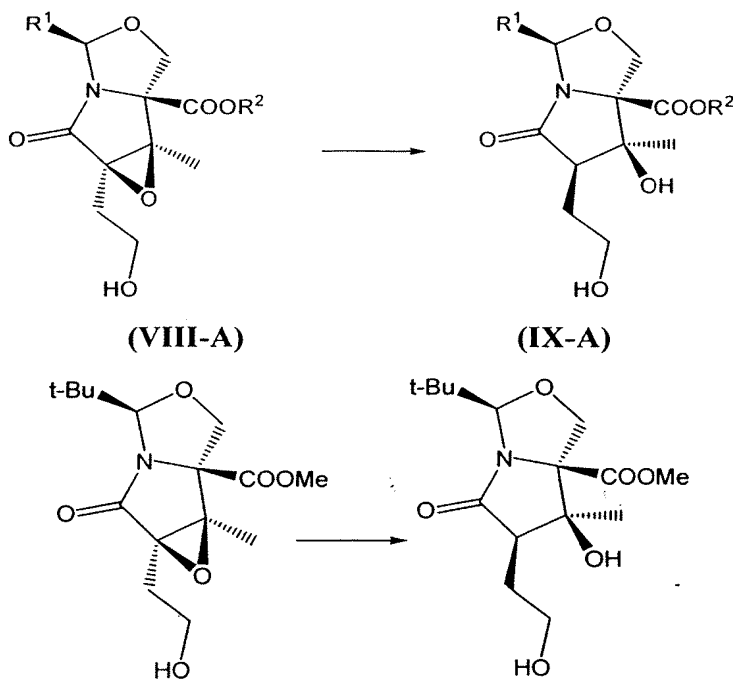
[0142] In an embodiment, the compounds of formulae (VII) and (VIII) can have the following structures and stereochemistry:





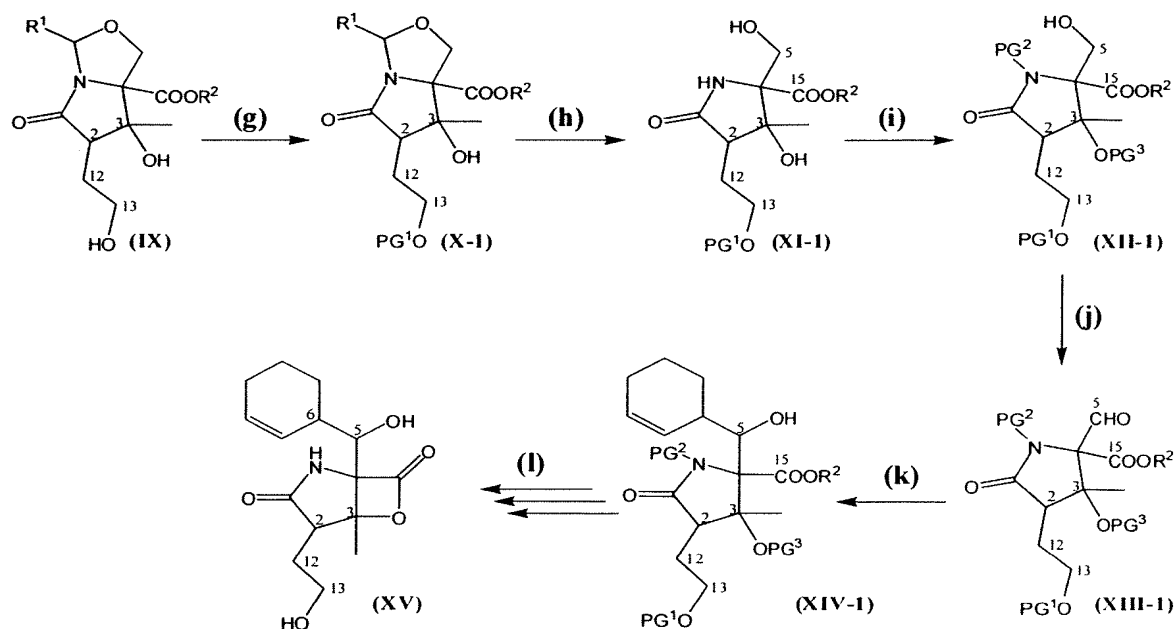
[0143] As shown in step (f), the epoxide ring can be opened to form a compound of formula (IX). The epoxide ring may be cleaved using an appropriate reducing agent. For example, the epoxide ring may be opened using samarium iodide. In some embodiments, cleavage of the epoxide can generate an (*R*)-stereocenter at C-2 and an (*S*)-stereocenter at C-3. As stated previously, by forming the epoxide stereospecifically and then cleaving the epoxide the desired chirality at C-2 and C-3 can be obtained. Furthermore, additional steps that may be required to attain the stereochemistry at the C-2 and/or C-3 using another method can be avoided.

[0144] Examples of the structure and stereochemistry of compounds of formulae (VIII) and (IX) are shown below:



[0145] As shown in Figures 2-3 and 4a-d, several methods can be used to form a compound of formula (XV). One method for forming a compound of formula (XV) starting from a compound of formula (IX) is shown below in Scheme 9. An example of the synthesis of a compound of formula (XV) from a compound of formula (IX) is shown in Figures 4a-b.

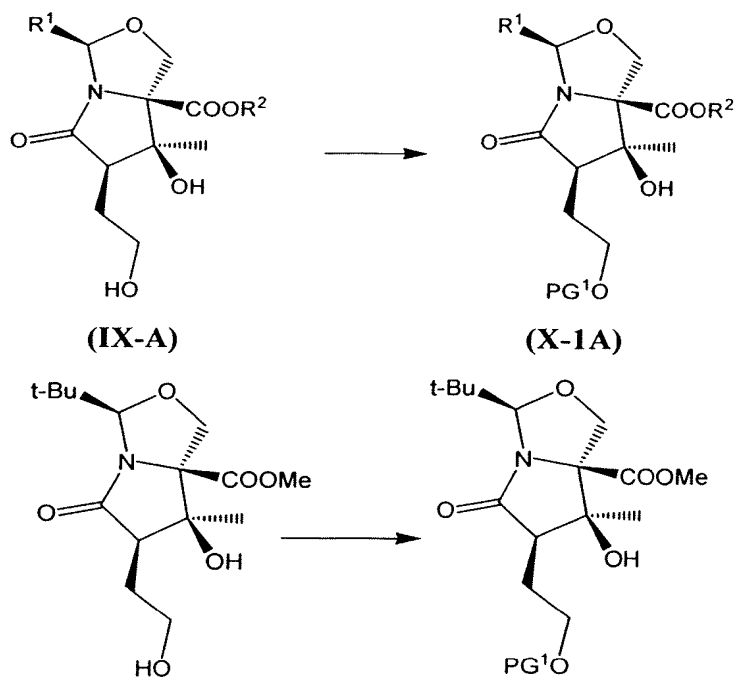
Scheme 9



[0146] If desired, the C-13 primary hydroxy group of a compound of formula (IX) can be protected using a protecting group moiety to form a compound of formula (X-1), as shown in step (g) of Scheme 9. In some embodiments, PG¹ can be selected from substituted or unsubstituted arylcarbonyls (e.g., benzoyl); substituted or unsubstituted alkylcarbonyls (e.g. acetyl); substituted or unsubstituted arylalkylcarbonyls; substituted or unsubstituted alkoxy carbonyls; substituted or unsubstituted aryloxy carbonyls; substituted methyl ether (e.g. methoxymethyl); substituted ethyl ether; substituted or substituted benzyl (e.g. benzyl, 4-methoxybenzyl); tetrahydropyranyl ether; silyl ethers (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, or t-butyldiphenylsilyl); esters, carbonates (e.g. methoxymethylcarbonate); and sulfonates (e.g. mesylate, tosylate). In some embodiments, the R¹ group can be hydrogen, unsubstituted or substituted C₁₋₆ alkyl or unsubstituted or substituted aryl. In an embodiment, the R¹ group can be t-butyl. In some embodiments, R² can be selected from

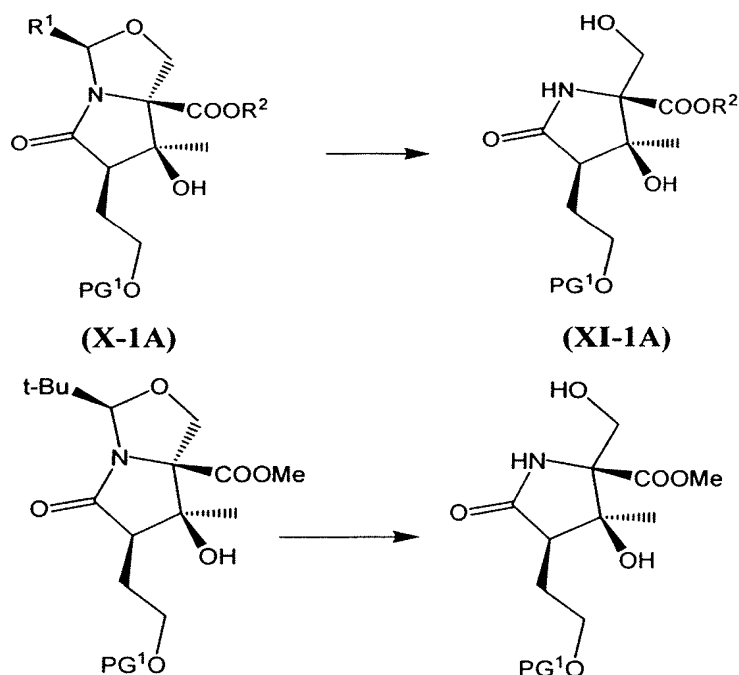
hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, R^2 can be an unsubstituted or substituted C_{1-6} alkyl. In an embodiment, R^2 can be methyl.

[0147] In an embodiment, compounds of formulae (IX) and (X-1) can have the following structures and stereochemistry:



[0148] As shown in step (h), the aминаl group of a compound of formula (X-1) can be cleaved to form a compound of formula (XI-1). In an embodiment, the aминаl can be cleaved using a suitable acid (e.g. triflic acid, HCl, PTSA, PPTS, TFA, camphor sulfonic acid).

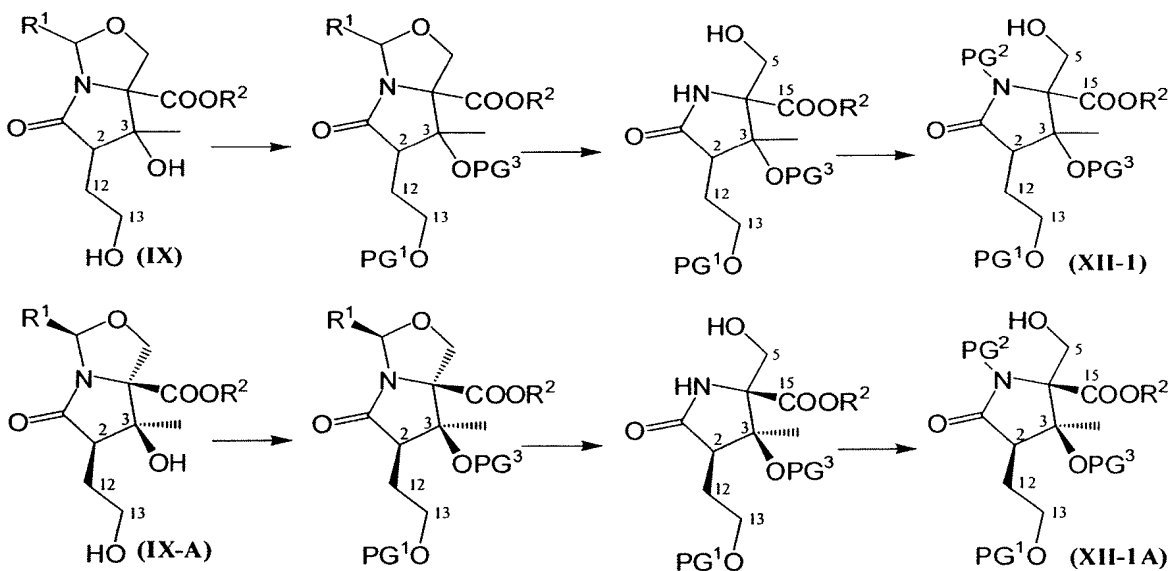
[0149] Exemplary structures and stereochemistry of the compounds of formulae (X-1) and (XI-1) are shown below:



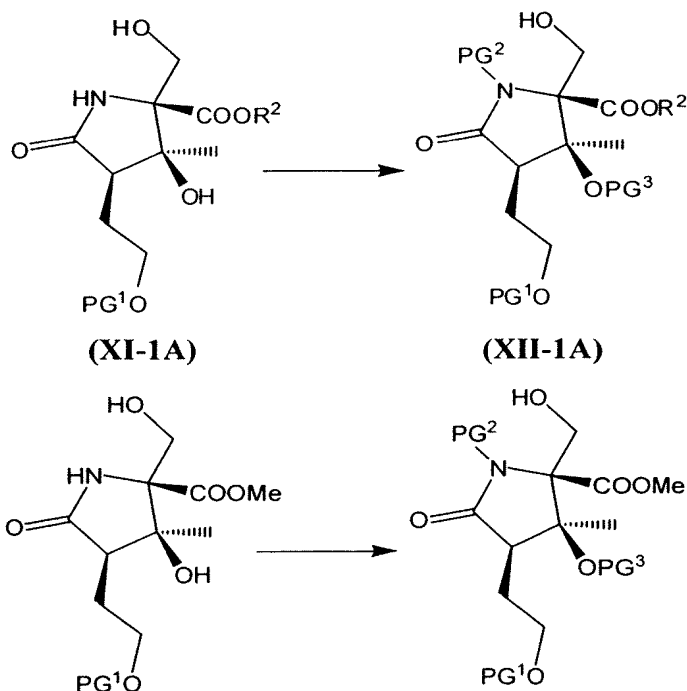
[0150] Optionally, the lactam nitrogen and/or the tertiary hydroxy group of a compound of formula (XI-1) may be protected using a protecting group moiety indicated by PG² and PG³, respectively. Examples of suitable protecting groups include, but are not limited to the following: substituted or unsubstituted arylcarbonyls (e.g., benzoyl); substituted or unsubstituted alkylcarbonyls (e.g. acetyl); substituted or unsubstituted arylalkylcarbonyls; substituted or unsubstituted alkoxy carbonyls; substituted or unsubstituted aryloxy carbonyls; substituted methyl ether (e.g. methoxymethyl); substituted ethyl ether; substituted or substituted benzyl (e.g. benzyl, 4-methoxybenzyl); tetrahydropyranyl ether; silyl ethers (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyl dimethylsilyl, or t-butyl diphenylsilyl); esters, carbonates (e.g. methoxymethyl carbonate); and sulfonates (e.g. mesylate, tosylate). In some embodiments, it may be desirable to protect the tertiary hydroxyl group and/or lactam nitrogen group to avoid undesirable side reactions and/or make isolation of the desired compounds easier. In an embodiment, the lactam nitrogen is protected to facilitate the stereospecific addition of the 2-cyclohexenyl moiety. As an example, by protecting the lactam nitrogen with a bulky protecting group such as benzyl groups, the 2-cyclohexenyl ring will add to C-5 to form an (*S*)-stereocenter. Moreover, having a bulky protecting

group on the lactam nitrogen also can facilitate in establishing an (*S*)-stereocenter at C-6. In some embodiments, PG² and PG³ are the same. In other embodiments, PG² and PG³ are different protecting groups. In an embodiment, the protecting groups, PG² and PG³, can be added almost simultaneously. In another embodiment, the protecting groups, PG² and PG³, can be added sequentially. For example, in some embodiments, PG² can be added before PG³. In other embodiments, PG³ can be added before PG². If protection of the lactam nitrogen and/or tertiary hydroxy group is unnecessary and/or undesired, the remaining steps of Scheme 9 can be carried out wherein PG² and PG³ are both hydrogen and the steps that show the addition and removal of the protecting group(s), PG² and/or PG³, can be excluded. Alternatively, the tertiary hydroxy group on C-3 can be protected in compounds previous to a compound of formula (XII-1). For example, the tertiary hydroxy group can be protected on a compound of formula (X-1) and/or a compound of formula (XI-1) using a suitable protecting group such as those described previously.

Scheme 9a

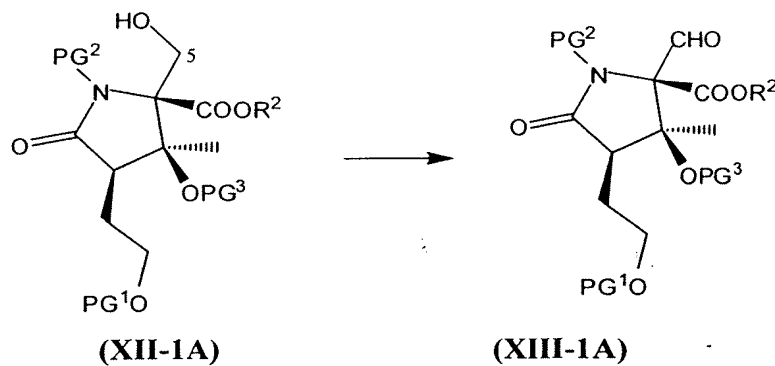


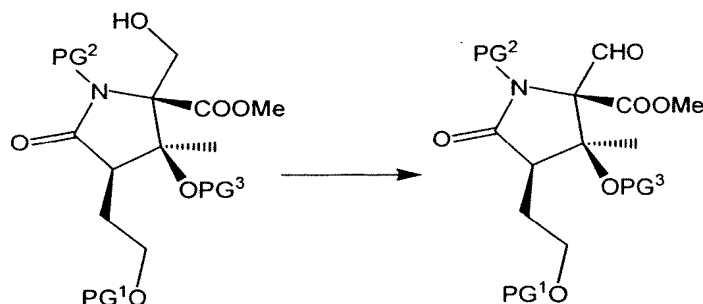
[0151] As an example, the compounds of formulae (XI-1) and (XII-1) may have the following structures and stereochemistry:



[0152] The C-5 primary hydroxy group of formula (XII-1) can be oxidized to an aldehyde to form a compound of formula (XIII-1) using an appropriate oxidizing agent. Appropriate oxidizing agents are disclosed herein. In an embodiment, the C-5 primary hydroxy group can be oxidized using Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, and/or PDC.

[0153] In an embodiment, the compounds of formulae (XII-1) and (XIII-1) may have the following structures and stereochemistry:



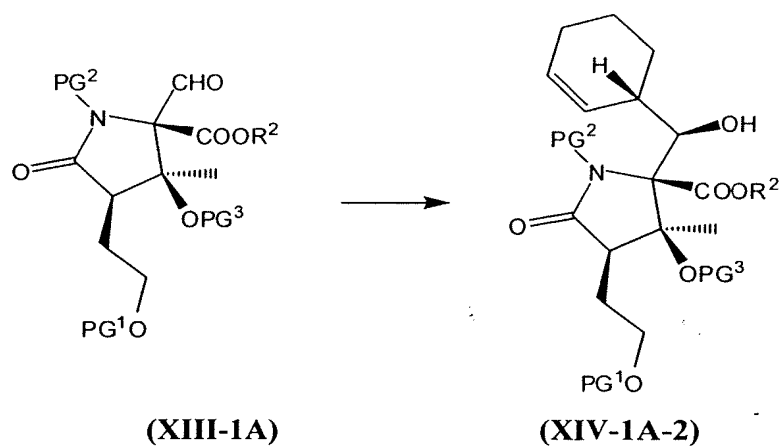
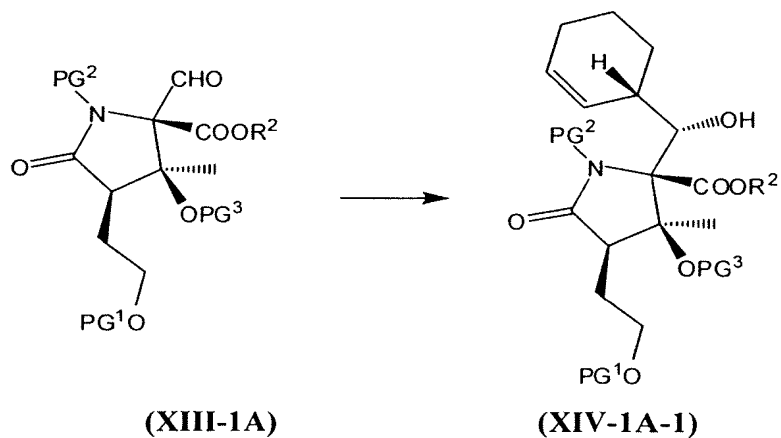
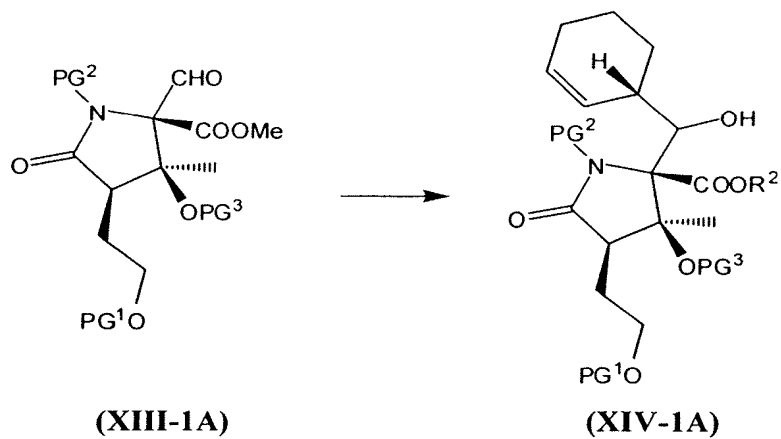


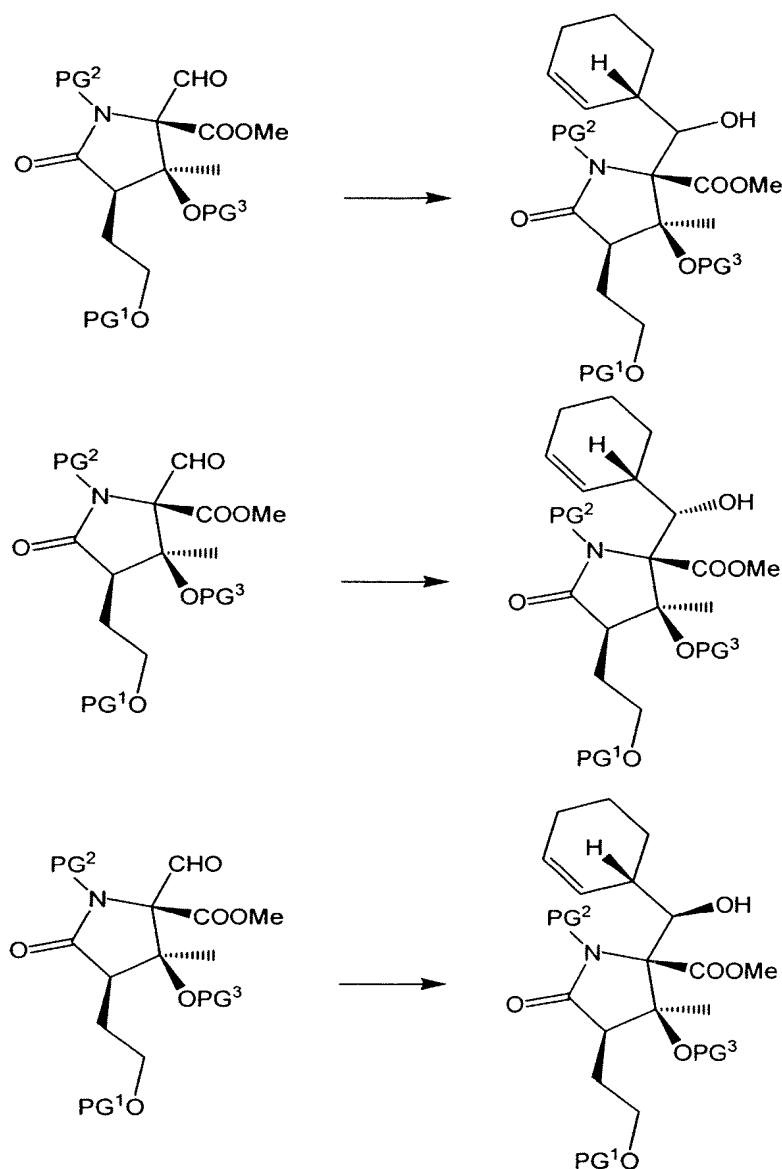
[0154] In step (k) of Scheme 9, a cyclohexenyl ring can be added to the C-5 position of a compound of formula (XIII-1) to form a compound of formula (XIV-1). The alkylation methods are known to those skilled in the art. For example, the addition of the cyclohexenyl ring may be accomplished using an organometallic moiety (e.g., zinc chloride) having a cyclohexenyl group.

[0155] A non-limiting list of suitable organometallic moieties include organomagnesium compounds, organolithium compounds, organotin compounds, organocuprates compounds, organozinc, and organopalladium compounds, metal carbonyls, metallocenes, carbene complexes, and organometalloids (e.g., organoboranes and organosilanes). In some embodiments, the organometallic moiety can be selected from 2-cyclohexenyl-MgR⁴, 2-cyclohexenyl-ZnR⁴, 2-cyclohexenyl-Li, (2-cyclohexenyl)_p-B(R⁴)_{3-p}, and (2-cyclohexenyl)_q-Sn(R⁴)_{4-q}; wherein R⁴ can be selected from halogen, or substituted or unsubstituted variants of the following: alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, isopinocampheyl, hydroxy, alkoxy, and carbonylalkoxy, wherein if more than one R⁴ is present, the R⁴ groups can optionally be bonded together to form an optionally substituted cycloalkyl (e.g., 9-BBN), optionally substituted cycloalkenyl, optionally substituted heteroalkyl or optionally substituted heteroalkenyl ring; p can be an integer from 1 to 3; and q can be an integer from 1 to 4. In an embodiment, the organometallic moiety can be (2-cyclohexenyl)_p-B(R⁴)_{3-p}. In some embodiments, the organometallic moiety can be (2-cyclohexenyl)_p-B(R⁴)_{3-p}, p is 1, and the two R⁴ groups are taken together to form an optionally substituted cycloalkyl. In an embodiment, the organometallic moiety can be 2-cyclohexenyl-MgR⁴. In some embodiments, the organometallic moiety can be 2-cyclohexenyl-MgR⁴ and R⁴ is a halogen (e.g., chlorine).

[0156] In some embodiments, the organometallic moiety can be 2-cyclohexenyl-ZnR⁴. In an embodiment, 2-cyclohexenyl-ZnR⁴ can be 2-cyclohexenyl-ZnCl

[0157] Exemplary structures and stereochemistry for the compounds of formulae (XIII-1) and (XIV-1) include:



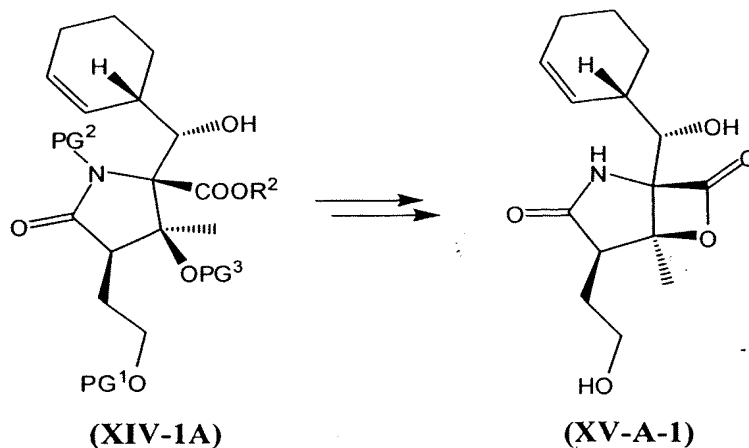


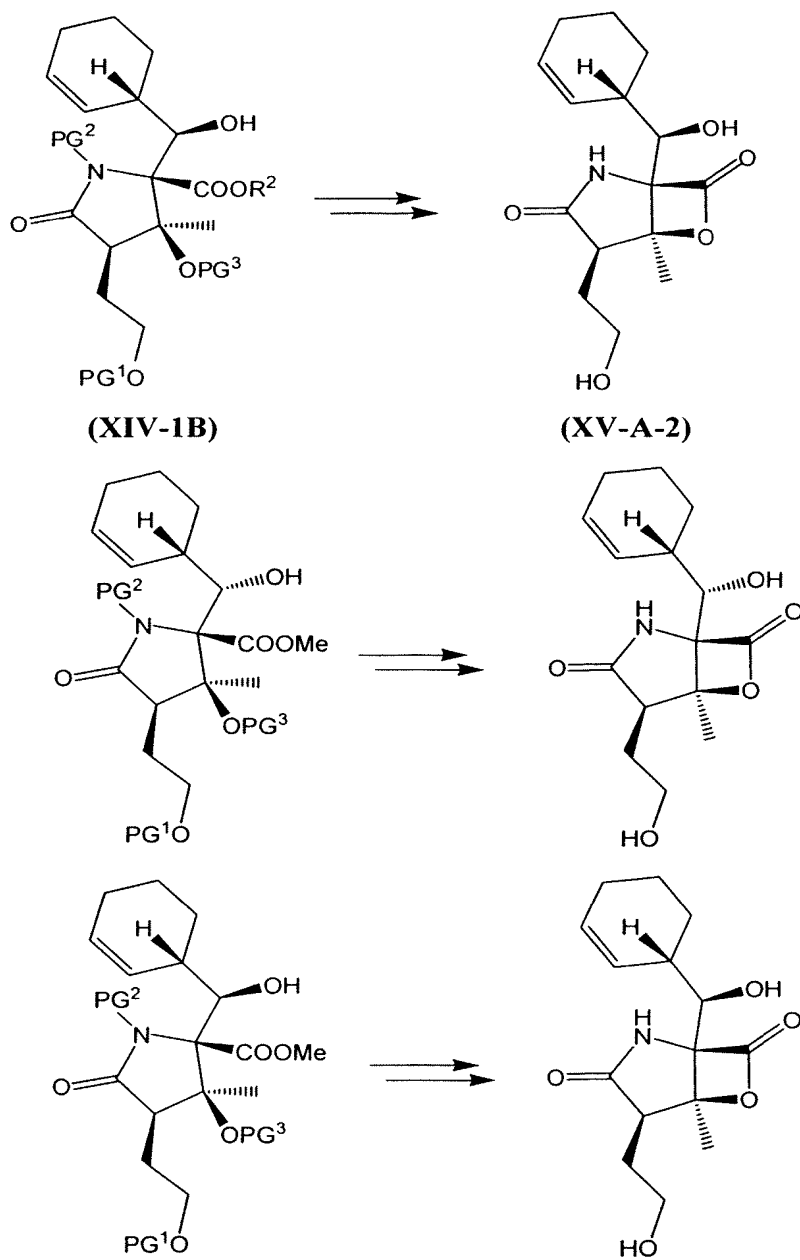
[0158] As shown in step (I) of Scheme 9, one or more of the protecting group moieties, if present, may be removed from a compound of formula (XIV-1). In some embodiments, PG¹, PG² and PG³ can be removed using an appropriate reagent(s). In an embodiment, PG¹, PG² and PG³ can be removed almost simultaneously. For example, PG¹, PG² and PG³ can be removed by the same reagent(s). In another embodiment, PG¹, PG² and PG³ can be removed sequentially. In some embodiments, PG¹ and PG³ can be removed and the lactam nitrogen can remain protected. The resulting compound of formula (XV) with a protected lactam nitrogen can be used to form Salinosporamide A

and analogs thereof as described herein. After formation of Salinosporamide A or an analog thereof, the protecting group on the lactam nitrogen can be removed. The protecting group, PG², can be removed using methods known to those skilled in the art. For example, PG² can be removed using one or more of the following reagents: 2,3-dichloro-5,6-dicyanobenzoquinone DDQ, ceric ammonium nitrate (CAN), TFA (trifluoroacetic acid) and hydrogen/Pd-C. Similarly, PG¹ and PG³ can be removed at any suitable time during the synthesis. In some embodiments, PG³ can be removed at any time before the formation of the 4-membered heterocyclic ring. Likewise, PG¹ can be removed anytime before the addition of the desired group to C-13.

[0159] A 4-membered heterocyclic ring can be formed using methods known to those skilled in the art to give a compound of formula (XV) as shown in step (I) in Scheme 9. For example, a beta-lactone can be formed using an appropriate base (e.g., BOPCl/pyridine, triethylamine) to induce lactonization. In an embodiment, the C-15 ester can first be transformed to a carboxylic acid, an activated acid (e.g., acid halide), or an activated ester (e.g., p-nitrophenyl ester, pentafluorophenyl ester, pentafluoroethyl ester, trifluoroethyl ester, trichloroethyl ester, a thioester, etc.) before being treated with an appropriate reagent to induce the lactonization reaction. In an embodiment, the C-15 carboxylic acid can be treated with an appropriate base to affect the lactonization reaction.

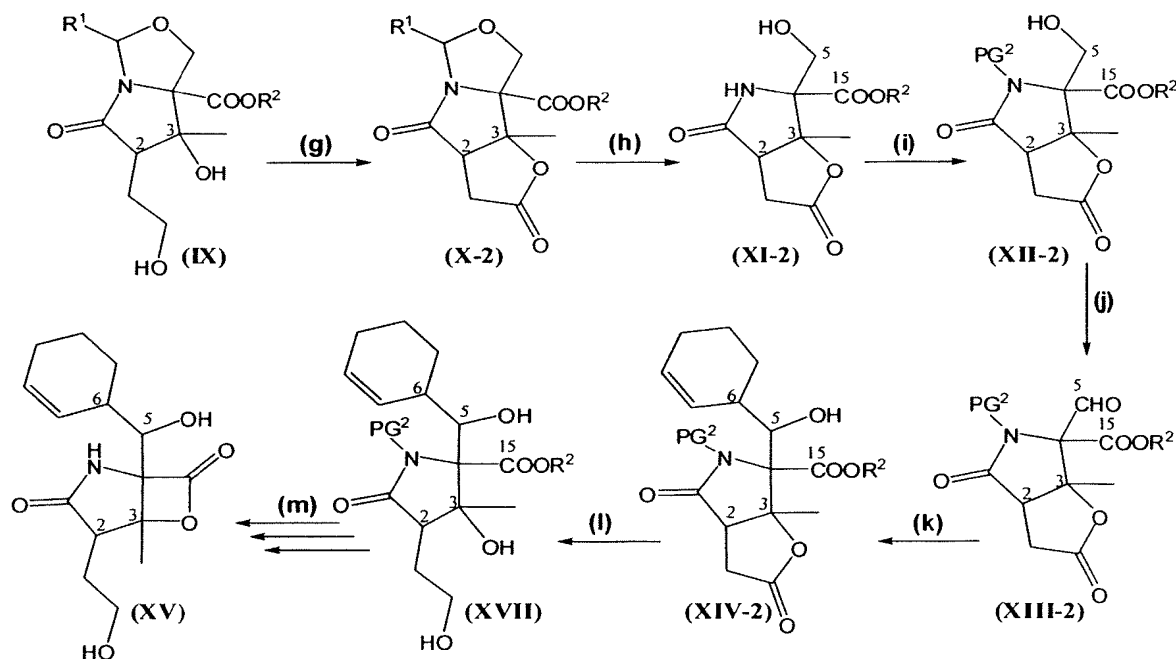
[0160] In an embodiment, compounds of formulae (XIV-1) and (XV) can have the following structure and stereochemistry:





[0161] An alternative method for forming a compound of formula (XV) from a compound formula (IX) is shown in Scheme 10. An example of this synthesis is shown in Figures 4a and 4c.

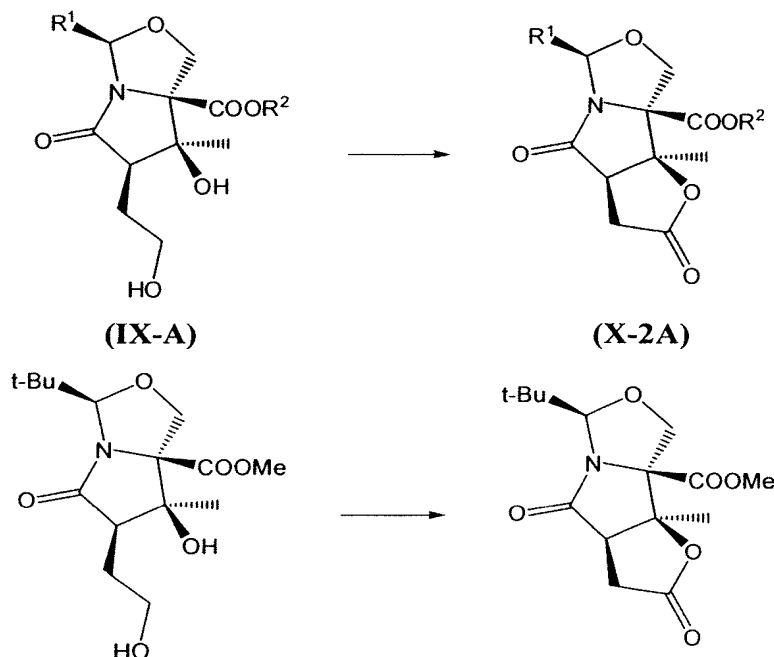
Scheme 10



[0162] As shown in step (g) in Scheme 10, a 5-membered lactone can be formed by reacting a compound of formula (IX) with an appropriate oxidizing agent. In some embodiments, the R¹ group can be hydrogen, unsubstituted or substituted C₁₋₆ alkyl or unsubstituted or substituted aryl. In an embodiment, the R¹ group can be t-butyl. In some embodiments, R² can be selected from hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, R² can be an unsubstituted or substituted C₁₋₆ alkyl. In an embodiment, R² can be methyl. Appropriate oxidizing agents include, but are not limited to, pyridinium chlorochromate (PCC), KMnO₄, CrO₃, Na₂Cr₂O₇. In an embodiment, the oxidizing agent can be pyridinium chlorochromate (PCC). The resulting oxidized compound can then undergo an intramolecular cyclization reaction to form a compound of formula (X-2). In some embodiment, the C-13 primary alcohol can be oxidized to an aldehyde. The aldehyde and C-3 tertiary alcohol can react together to form a hemi-acetal via an intramolecular cyclization reaction. The hemi-acetal can then be further oxidized to a lactone. In another embodiment, the C-13 primary alcohol can be oxidized to a carboxylic acid. The resulting carboxylic acid and C-3 tertiary alcohol then can cyclize together to form the 5-membered lactone. In an embodiment, forming the 5-membered

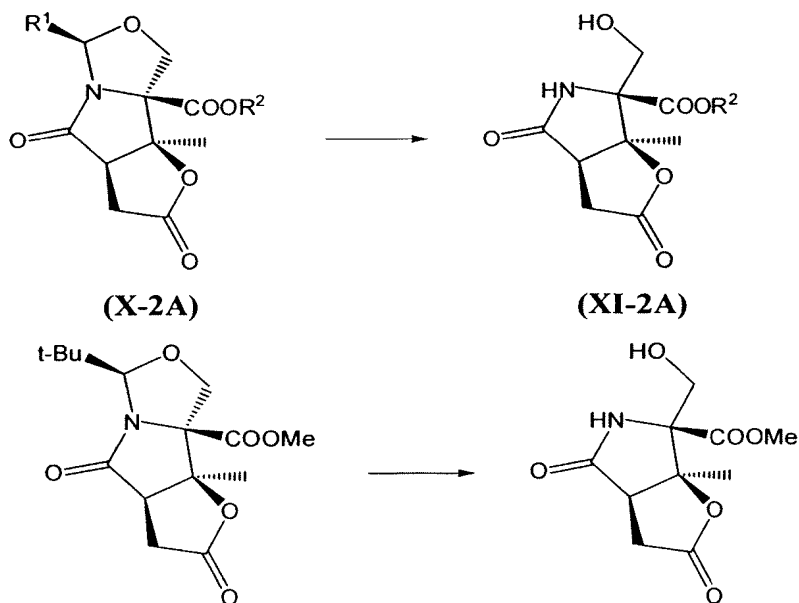
lactone can be advantageous to prevent the formation of unwanted side-products and/or simplify isolation of the desired compounds. In some embodiment, forming the 5-membered lactone can minimize the number of steps of the overall synthesis by protecting the C-13 and C-3 hydroxy groups with one moiety rather than multiple protecting groups which may need to be added and/or removed separately.

[0163] Examples of the structures and stereochemistry of the compounds of formulae (IX) and (X-2) are shown below.



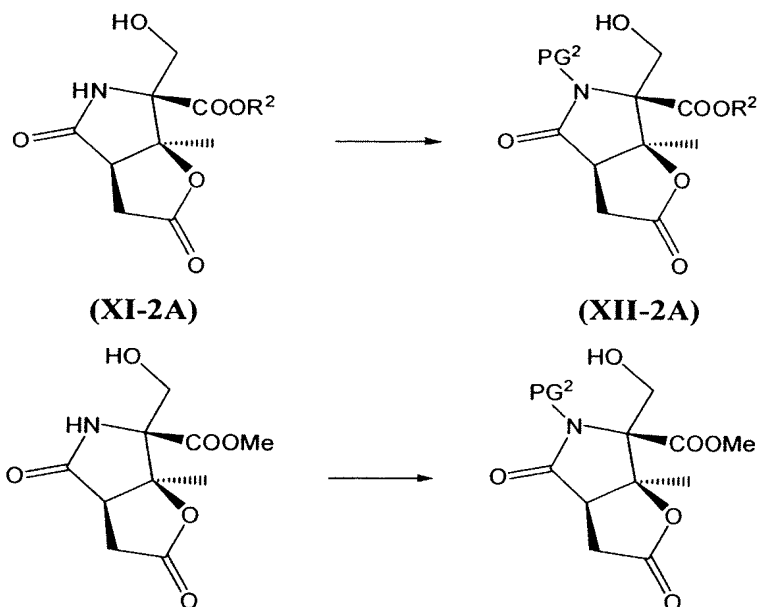
[0164] Similar to the reaction shown in Scheme 9, the aминаl group of a compound of formula (X-2) can be cleaved to form a compound of formula (XI-2). In some embodiments, the aминаl group can be cleaved using a suitable acid (e.g. triflic acid, HCl, PTSA, PPTS, TFA, camphor sulfonic acid).

[0165] In an embodiment, the compounds of formulae (X-2) and (XI-2) may have the following structures and stereochemistry:



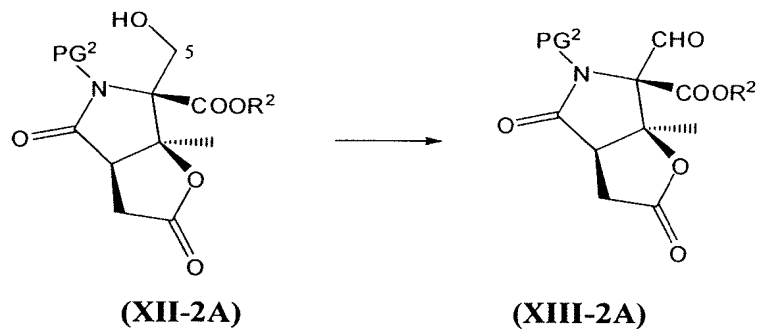
[0166] If desired or necessary, the lactam nitrogen of a compound of formula (XI-2) can be protected with a suitable protecting group moiety denoted by PG^2 . Examples of suitable protecting groups include, but are not limited to, benzyl, substituted benzyl, silyl, or methoxymethyl, as shown in step (i) of Scheme 10. If protection of the lactam nitrogen is undesired and/or not necessary, the remaining steps shown in Scheme 10 can be carried out in which PG^2 is replaced with a hydrogen, and the steps that show the addition and removal of the protecting group, PG^2 , can be excluded. As previously noted, the lactam can be protected to facilitate the stereospecific addition of the 2-cyclohexenyl moiety. For example, by protecting the lactam nitrogen with a bulky protecting group such as an optionally substituted benzyl group, the 2-cyclohexenyl ring will add to C-5 to form an (*S*)-stereocenter and an (*S*) stereocenter at C-6. In an embodiment, the protecting group on the lactam nitrogen can be a substituted benzyl group, for example, *p*-methoxybenzyl.

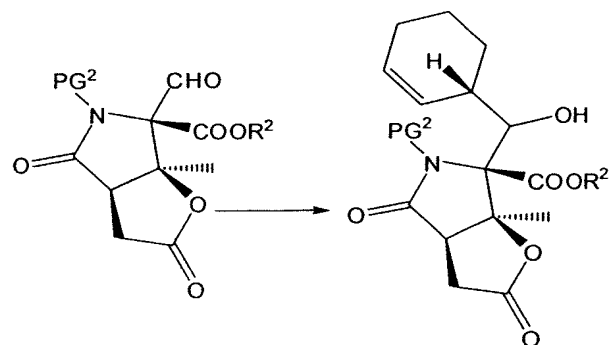
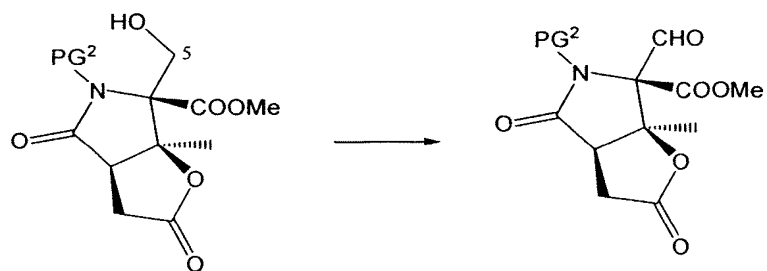
[0167] Exemplary structures and stereochemistry of compounds of formulae (XI-2) and (XII-2) are shown below:



[0168] Steps (j) and (k) shown in Scheme 10 can be carried out using reactions and conditions similar to those described above for steps (j) and (k) of Scheme 9.

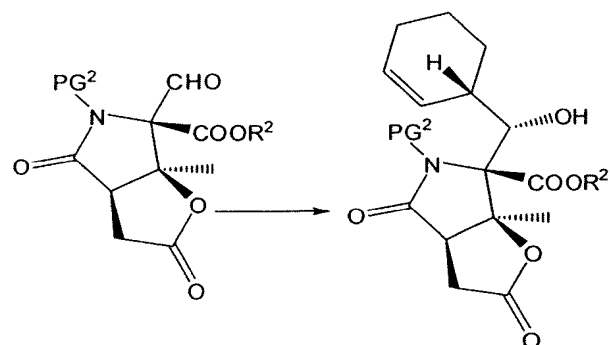
[0169] In an embodiment, the compounds of formulae (XII-2), (XIII-2) and (XIV-2) can have the following structures and stereochemistry.





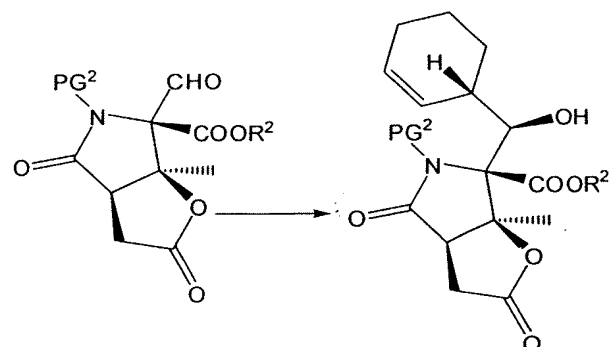
(XIII-2A)

(XIV-2A)



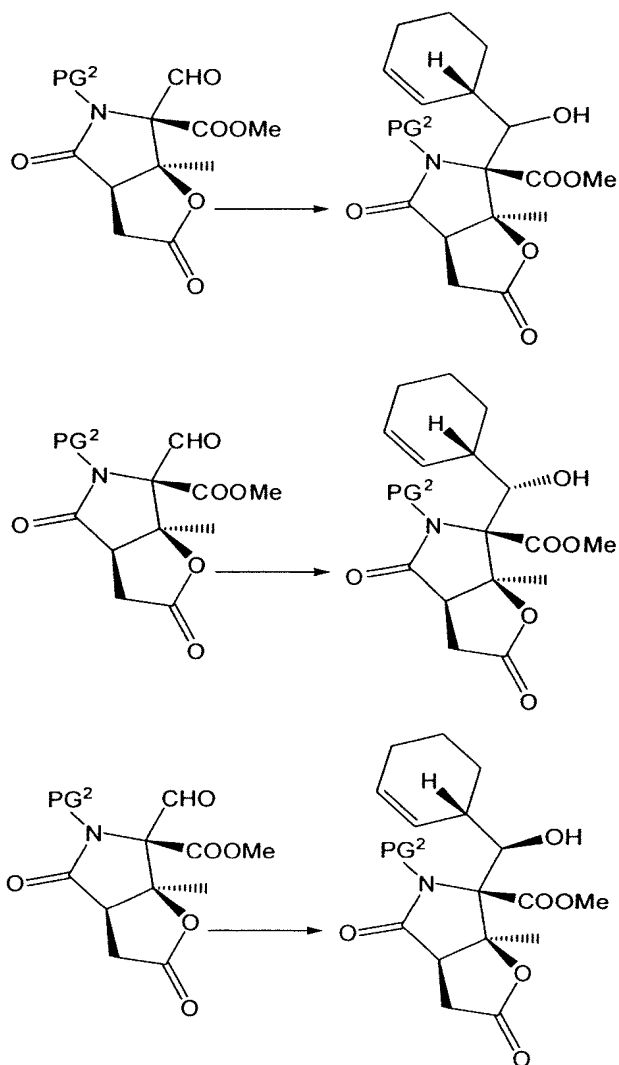
(XIII-2A)

(XIV-2A-1)



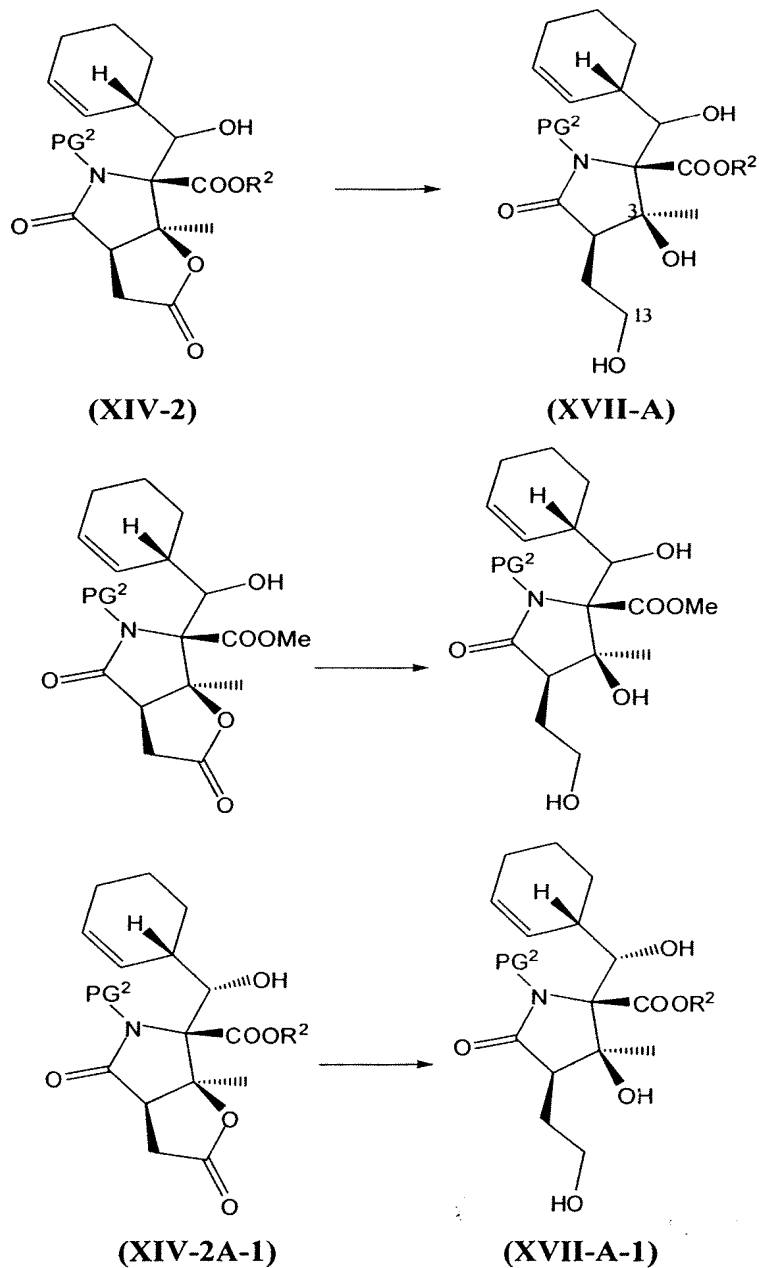
(XIII-2A)

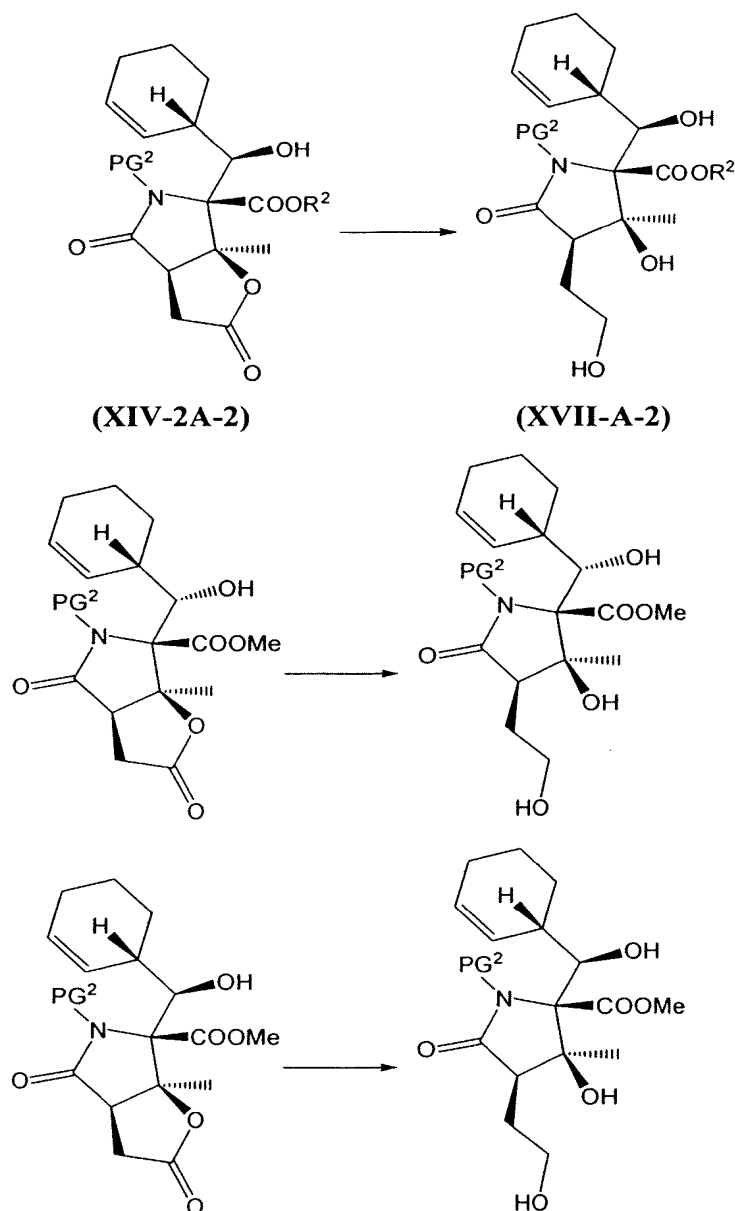
(XIV-2A-2)



[0170] As shown in step (l) in Scheme 10, the 5-membered lactone of a compound of formula (XIV) can be cleaved to form a compound of formula (XVII). Methods and reagents that can be used to cleave the lactone are known to those skilled in the art. In an embodiment, the 5-membered lactone can be cleaved using an appropriate reducing agent. Suitable reducing agents include, but are not limited to, NaBH_4 and LiAlH_4 . In some embodiments, the 5-membered lactone can be opened via a reductive ring opening reaction using an appropriate reducing agent (e.g., NaBH_4). Cleavage of the lactone under reducing conditions results in the formation of a primary alcohol at C-13 and a tertiary alcohol at C-3.

[0171] In an embodiment, the compounds of formulae (XIV-2) and (XVII) may have the following structures and stereochemistry:

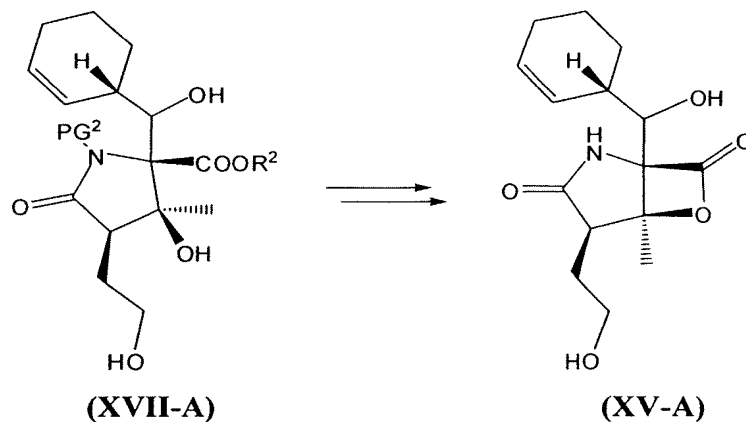


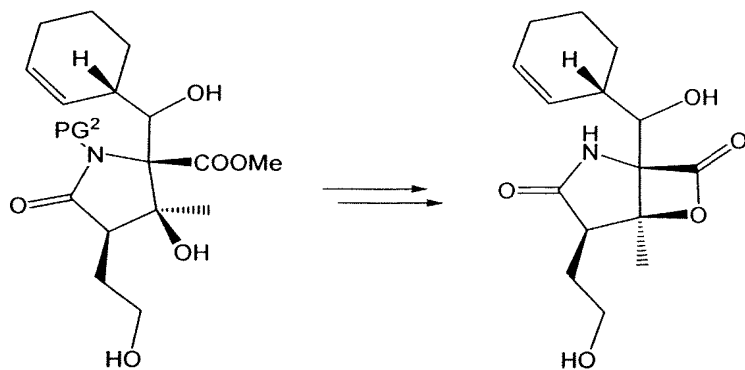
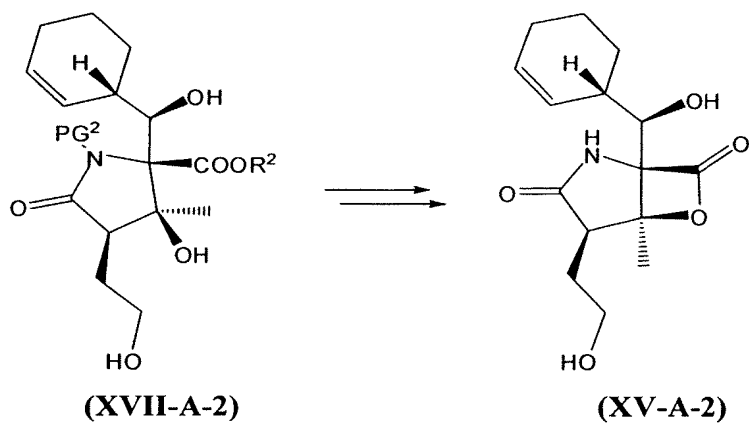
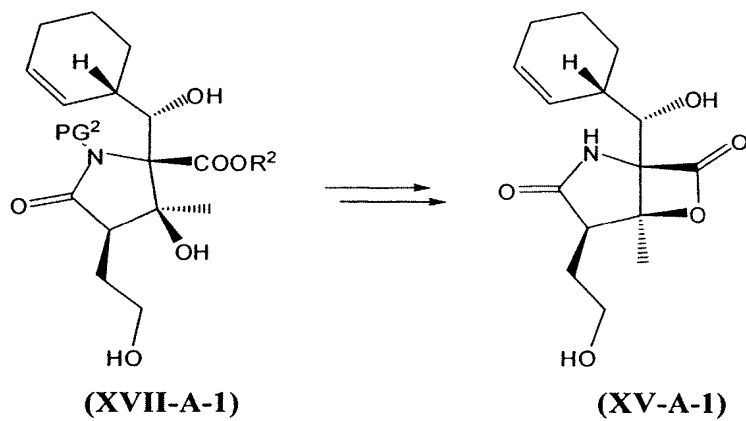


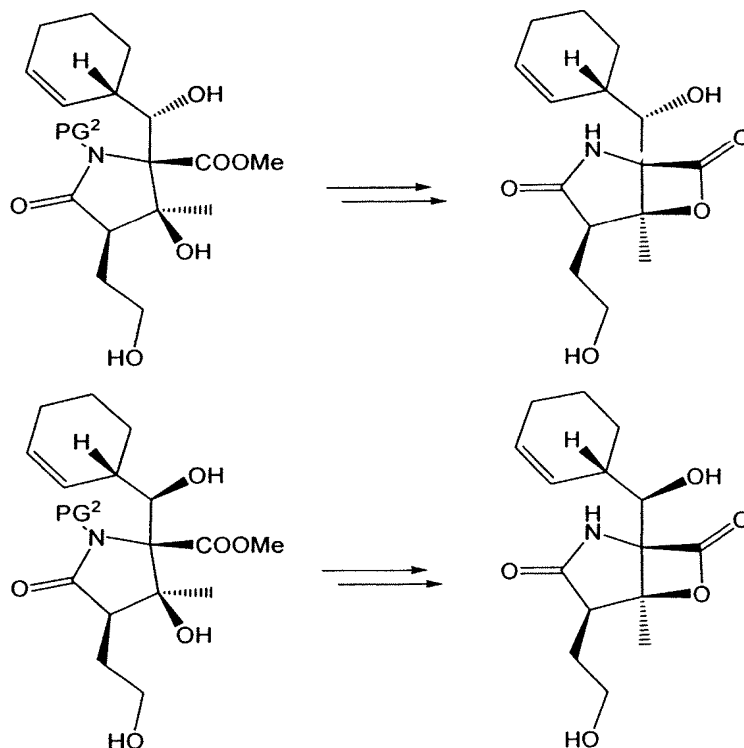
[0172] Starting with a compound of formula (XVII), the beta-lactone present in a compound of formula (XV) can be formed as described previously. For example, a lactone can be formed using an appropriate base (e.g., BOPCl/pyridine, triethylamine) to induce lactonization. Additionally, if the lactam is protected, the protecting group can be removed using suitable reagents and conditions. Examples of suitable reagent(s) for removing the protecting group PG^2 , include, but are not limited to, 2,3-dichloro-5,6-dicyanobenzoquinone DDQ, ceric ammonium nitrate (CAN), TFA (trifluoroacetic acid)

and hydrogen/Pd-C. Alternatively, if present, the lactam nitrogen protecting group can be removed anytime, for example, after the addition of the cyclohexenyl ring. Thus, the protecting group denoted by PG², can be removed using methods known to those skilled in the art, such as those described herein, from compounds of formulae (XIII-2) and (XIV-2). In some embodiments, the lactam nitrogen can remain protected and compounds of the general structure of compounds of formulae (XV) and (XVI) with a protected lactam nitrogen can be formed using the methods and reagents described herein. In the instances where the lactam nitrogen remains protected during the formation of compounds of the general structure of compounds of formulae (XV) and (XVI), the lactam nitrogen protecting group can be removed at anytime using the methods known to those skilled in the art. For example, the lactam nitrogen can be removed before formation of the beta-lactone ring, after formation of the beta-lactone ring but before replacement of the C-13 hydroxy, or after replacement of the C-13 hydroxy.

[0173] Examples of the structures and stereochemistry of compounds of formula (XVII) and (XV) include the following:

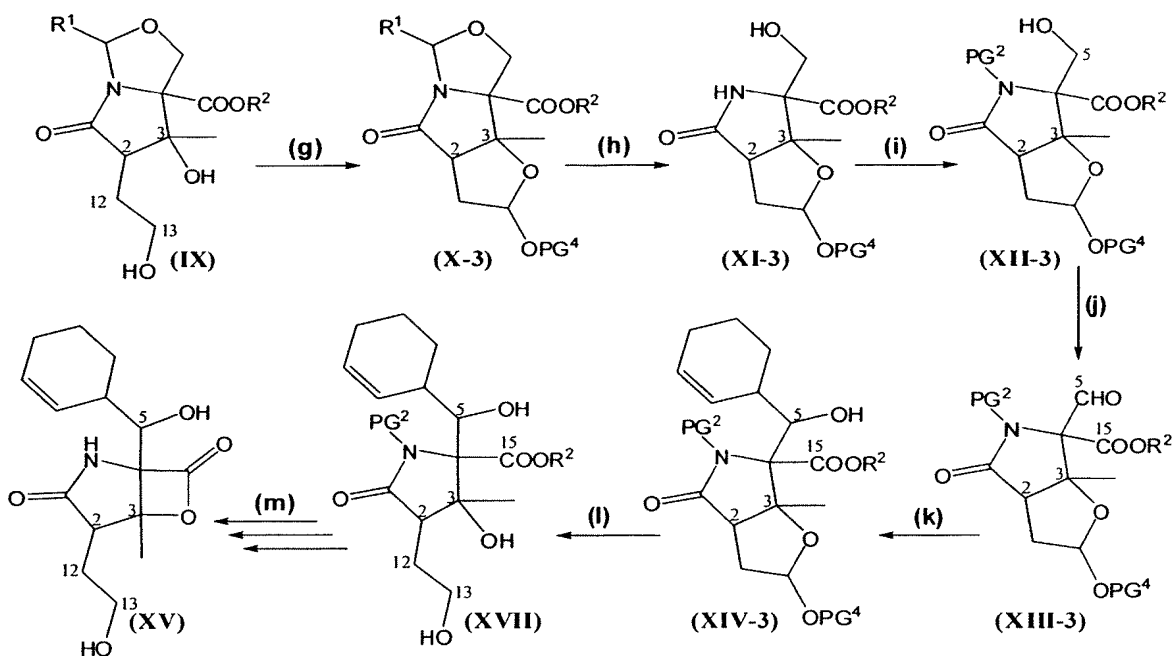






[0174] A compound of formula (XV) can also be synthesized starting with a compound of formula (IX) as shown in Scheme 11 and described below. One example of the synthesis of a compound of formula (XV) from a compound of formula (IX) is shown in Figures 4a and 4d.

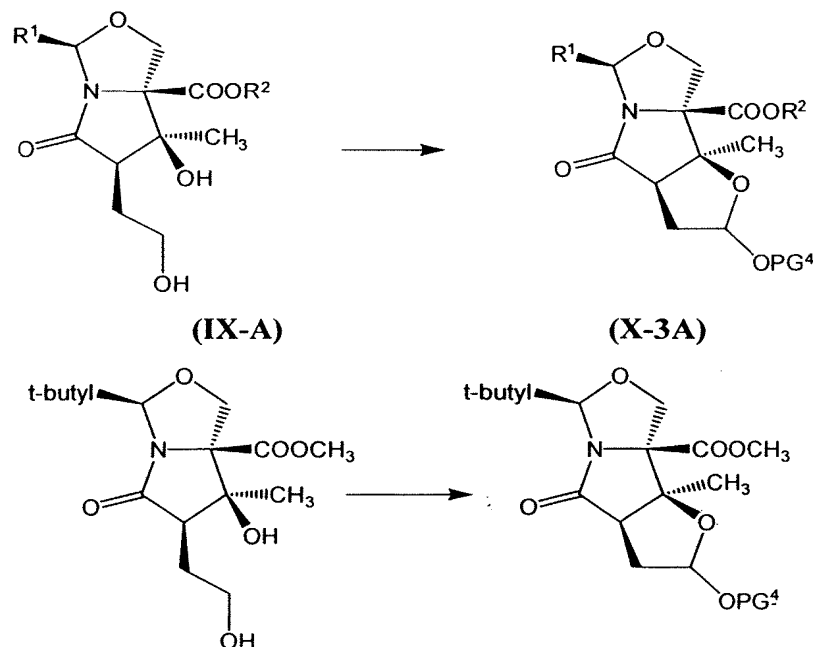
Scheme 11



[0175] As shown in Scheme 11, C-13 and oxygen of the C-3 tertiary alcohol of a compound of formula (IX) can be cyclized together to form a hemi-acetal. In an embodiment, the C-13 primary alcohol of a compound of formula (IX) can be oxidized to an aldehyde. The aldehyde and C-3 secondary alcohol then can react together and cyclize to form the hemi-acetal. In an embodiment, a method for obtaining a compound of formula (X-3) from a compound of formula (IX) includes reacting a compound of formula (IX) with a suitable oxidant or oxidant combination, such as Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, and PDC. In an embodiment, forming a hemi-acetal can be advantageous to prevent the formation of unwanted side-products and/or simplify isolation of the desired compounds. In some embodiments, the R¹ group can be hydrogen, unsubstituted or substituted C₁₋₆ alkyl or unsubstituted or substituted aryl. In an embodiment, the R¹ group can be t-butyl. In some embodiments, R² can be selected from hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl. In some embodiments, R² can be an unsubstituted or substituted C₁₋₆ alkyl. In an embodiment, R² can be methyl.

[0176] Optionally, the hemi-acetal can be converted to an acetal by protecting the hydroxy group of the hemi-acetal using a suitable protecting group denoted by PG⁴. Suitable protecting groups include, but are not limited to, substituted or unsubstituted arylcarbonyls (e.g., benzoyl); substituted or unsubstituted alkylcarbonyls (e.g. acetyl); substituted or unsubstituted arylalkylcarbonyls; substituted or unsubstituted alkoxy carbonyls; substituted or unsubstituted aryloxy carbonyls; substituted methyl ether (e.g. methoxymethyl); substituted ethyl ether; substituted or substituted benzyl (e.g. benzyl, 4-methoxybenzyl); tetrahydropyranyl ether; silyl ethers (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, or t-butyldiphenylsilyl); esters, carbonates (e.g. methoxymethylcarbonate); and sulfonates (e.g. mesylate, tosylate). . In an embodiment, the protecting group PG⁴ can be a benzyl group. If the hydroxy group of the hemi-acetal is not protected, a compound of formula (XV) can be obtained from a compound of formula (IX) following the steps shown in Scheme 11 excluding the addition and removal of the protecting group denoted by PG⁴.

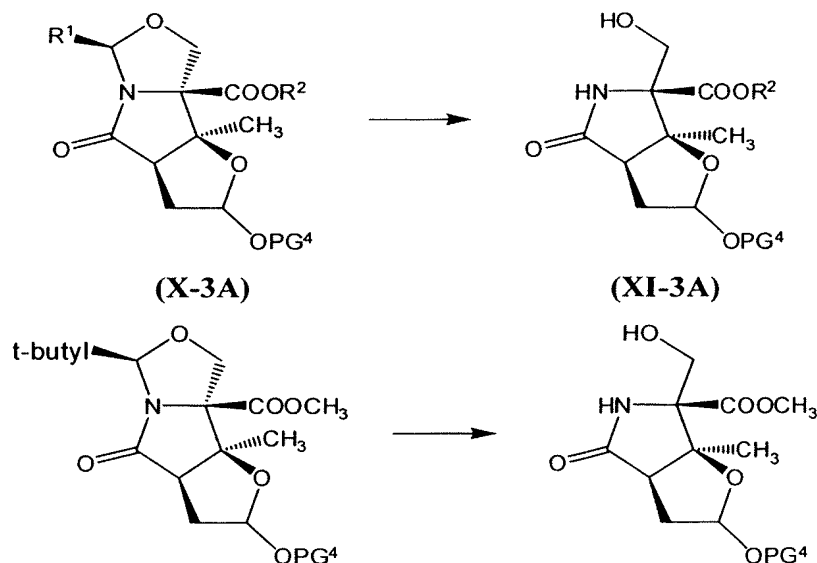
[0177] Examples of compounds of formulae (IX) and (X-3) include the following:



[0178] As shown in step (h), the aminal group of a compound of formula (X-3) can be cleaved to form a compound of formula (XI-3). In some embodiments, the

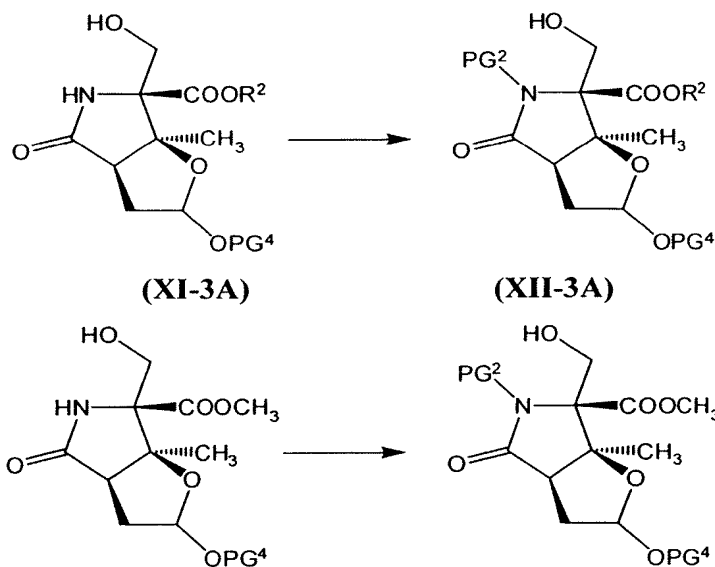
aminal group can be cleaved using a suitable acid (e.g. triflic acid, HCl, PTSA, PPTS, TFA, camphor sulfonic acid).

[0179] In some embodiments, the compounds of formula (X-3) and (XI-3) can be the structures and stereochemistry shown below.

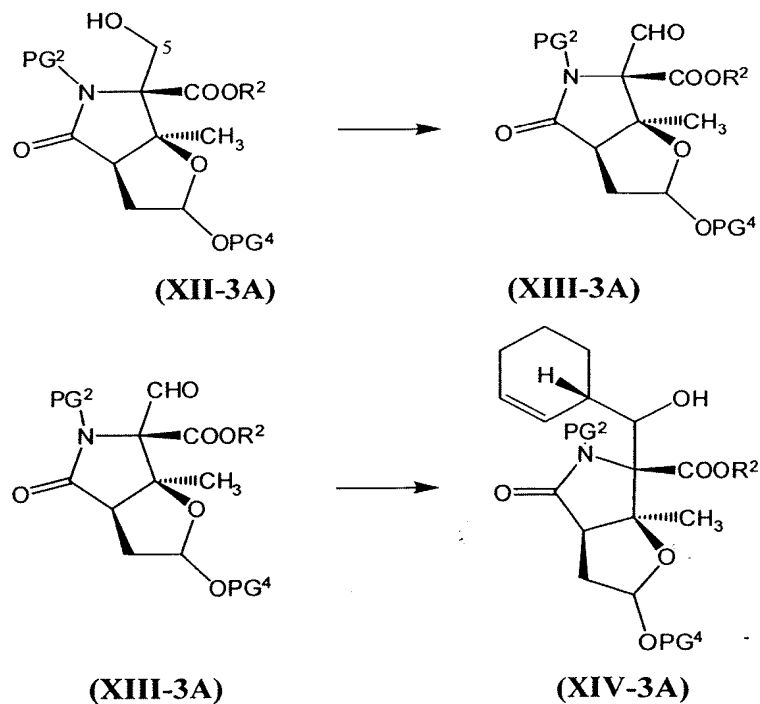


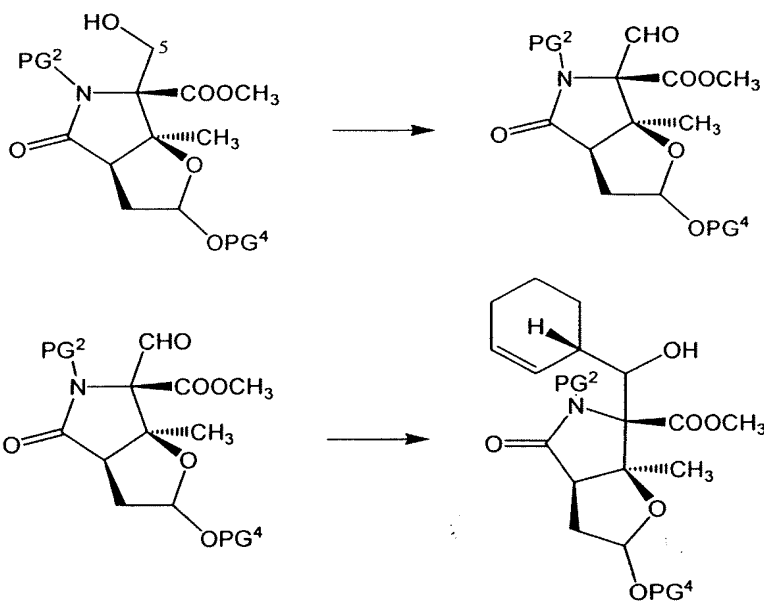
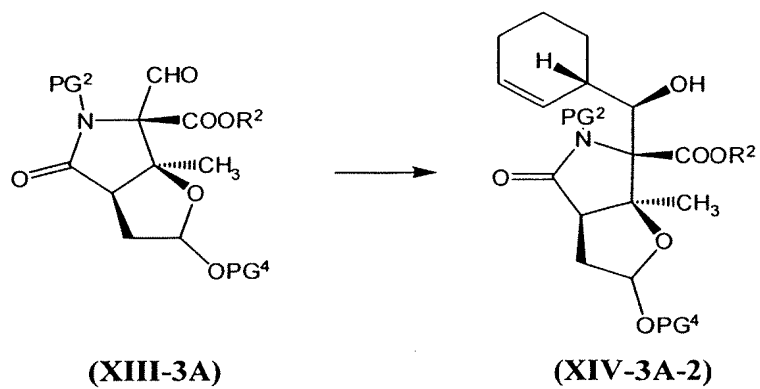
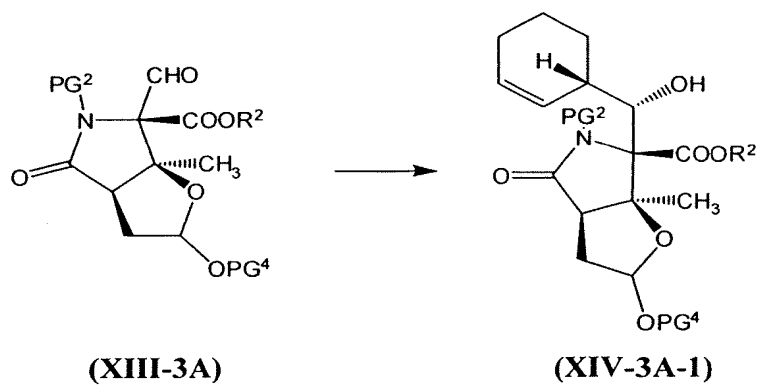
[0180] In some embodiments, the lactam nitrogen of a compound of formula (XI-3) can be protected with an appropriate protecting group (denoted by PG²) if desired and/or necessary. Suitable protecting groups include, but are not limited to, benzyl, substituted benzyl, t-butoxycarbonyl (t-Boc), Benzyloxycarbonyl (Cbz), silyl, or methoxymethyl. If protection of the lactam nitrogen is undesired and/or not necessary, the remaining steps shown in Scheme 11 can be carried out in which PG² is replaced with a hydrogen, and the steps that show the addition and removal of the protecting group, PG², can be excluded. As previously noted, the lactam nitrogen can be protected to facilitate the stereospecific addition of the 2-cyclohexenyl moiety such that the 2-cyclohexenyl group adds to form an (*S*)-stereocenter at C-5. Moreover, protecting the lactam nitrogen can also establish an (*S*) stereocenter at C-6. In an embodiment, the protecting group on the lactam nitrogen can be an optionally substituted benzyl group, for example, *p*-methoxybenzyl.

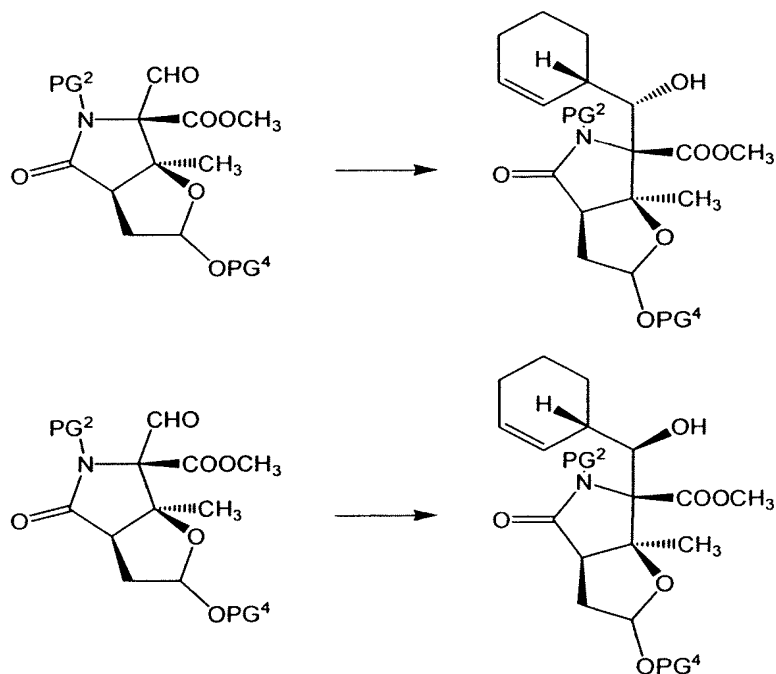
[0181] Exemplary structures and stereochemistry of compounds of formulae (XI-3) and (XII-3) are shown below:



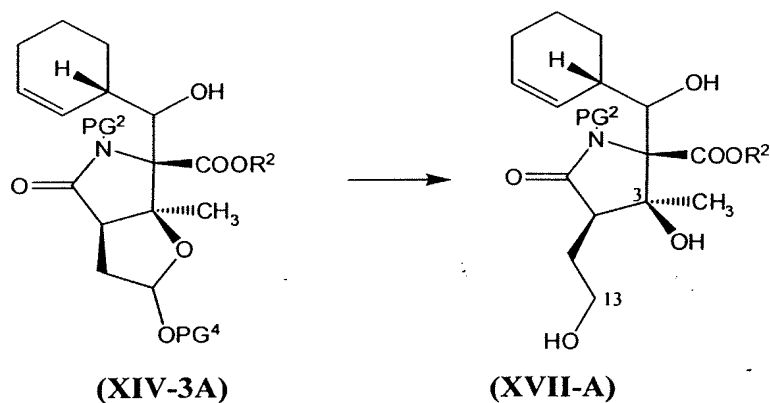
[0182] After formation of the acetal ring, steps (j), and (k) in Scheme 11 can be carried out similarly as described in steps (j), and (k) in Scheme 10. In an embodiment, the compounds of formulae (XIII-3) and (XIV-3) can have the following structures and stereochemistry.

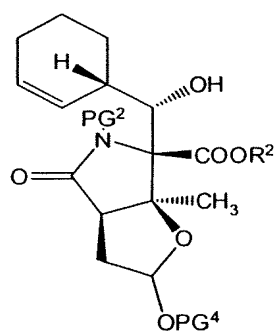




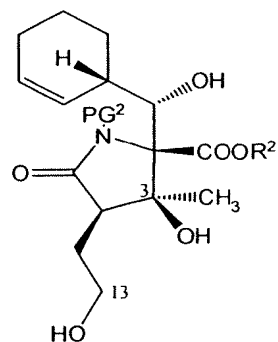
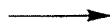


[0183] For step (I) shown in Scheme 11, any protecting group, denoted by PG^4 , present on the acetal ring can be removed and the ring can be opened using reductive methods and reagents known to those skilled in the art to give a hydroxy group attached to C-13 and another hydroxy group attached to C-3. In some embodiments, when PG^4 is benzyl, the benzyl group can be removed using sodium metal and liquid ammonium. In an embodiment, the acetal ring can be cleaved using a suitable reducing reagent such as sodium borohydride.

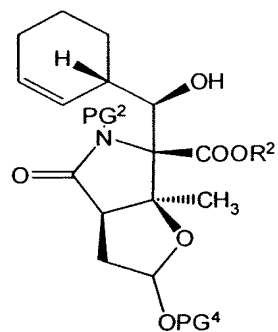




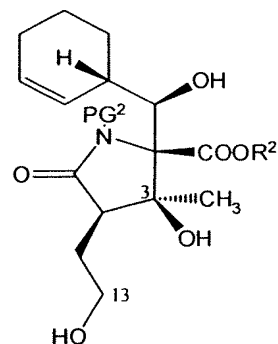
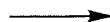
(XIV-3A-1)



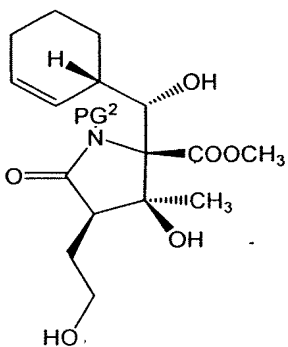
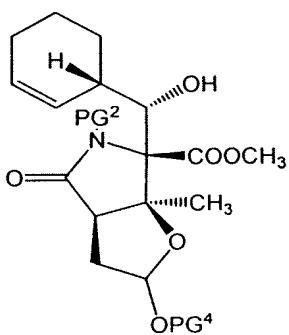
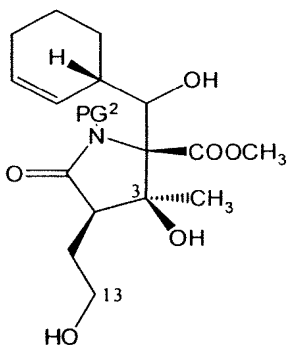
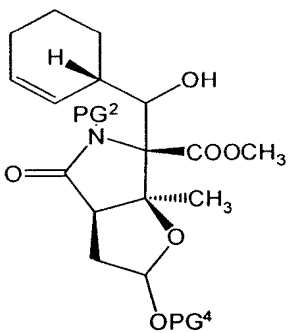
(XVII-A-1)

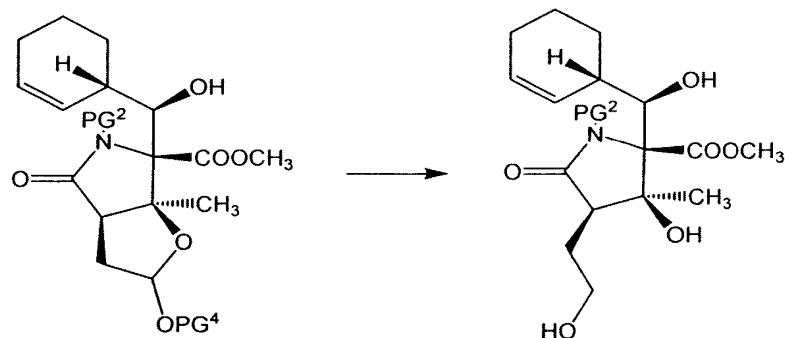


(XIV-3A-2)



(XVII-A-2)

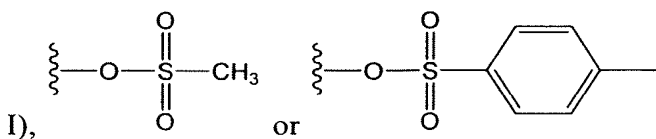




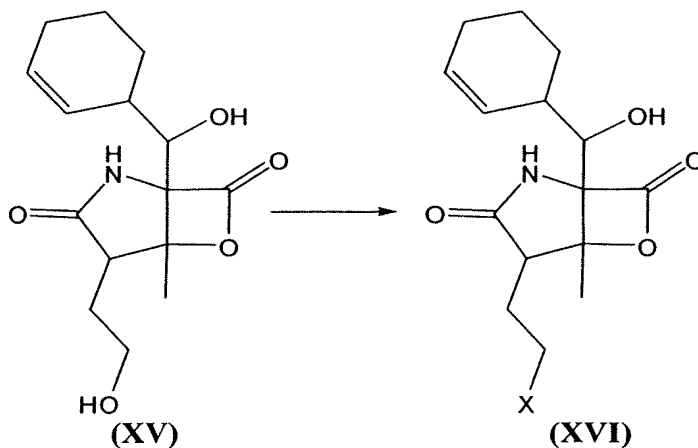
[0184] To obtain a compound of formula (XV), the 4-membered heterocyclic ring can be formed starting with a compound of formula (XVII) via a lactonization reaction. Methods for inducing the lactonization reaction have been described previously. In embodiment, a beta-lactone can be formed using an appropriate base (e.g., BOPCl/pyridine, triethylamine) to induce lactonization. Additionally, if the lactam nitrogen is protected, the protecting group can be removed using suitable reagents and conditions. In some embodiments, the lactam nitrogen protecting group can be removed at anytime, for example, after the addition of the cyclohexenyl ring. Thus, the protecting group denoted by PG², can be removed using methods known to those skilled in the art, such as those described herein, from compounds of formulae (XIII-3) and (XIV-3). . In some embodiments, the lactam nitrogen can remain protected and compounds of the general structure of compounds of formulae (XV) and (XVI) with a protected lactam nitrogen can be formed using the methods and reagents described herein. In the instances where the lactam nitrogen remains protected during the formation of compounds of the general structure of compounds of formulae (XV) and (XVI), the lactam nitrogen protecting group can be removed at anytime using the methods known to those skilled in the art. For example, the lactam nitrogen can be removed before formation of the beta-lactone ring, after formation of the beta-lactone ring but before replacement of the C-13 hydroxy, or after replacement of the C-13 hydroxy.

[0185] As shown in Scheme 12, a compound of formula (XV) can be further transformed by replacing the primary hydroxy group of the compound of formula (XV)

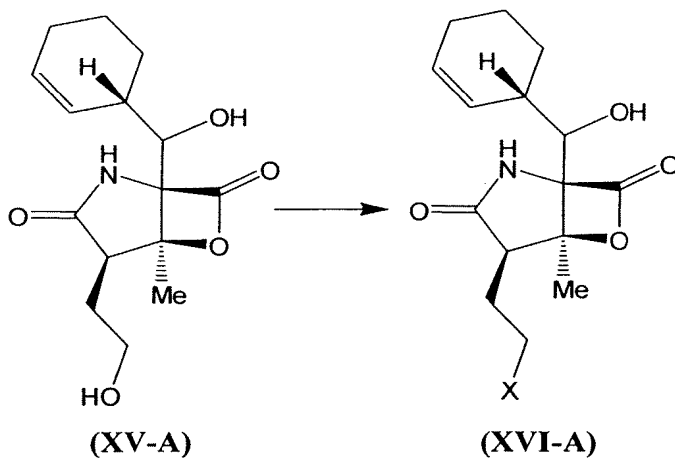
to form a compound of formula (XVI), wherein X can be a halogen (e.g., F, Cl, Br, and

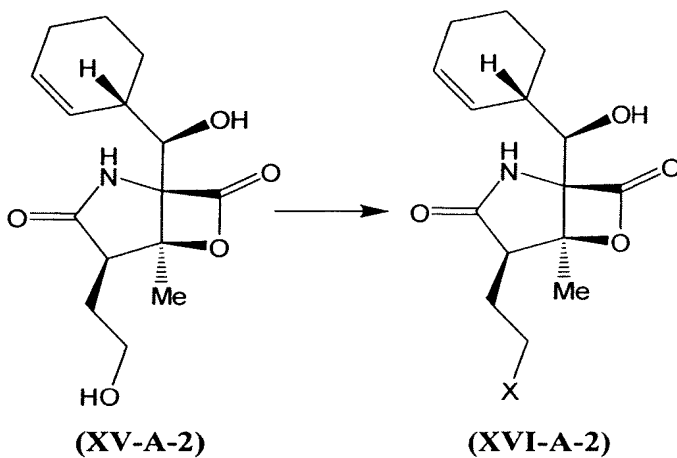
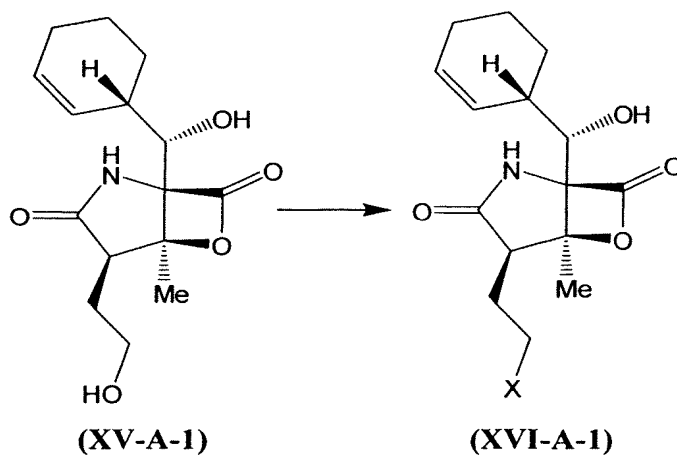


Scheme 12

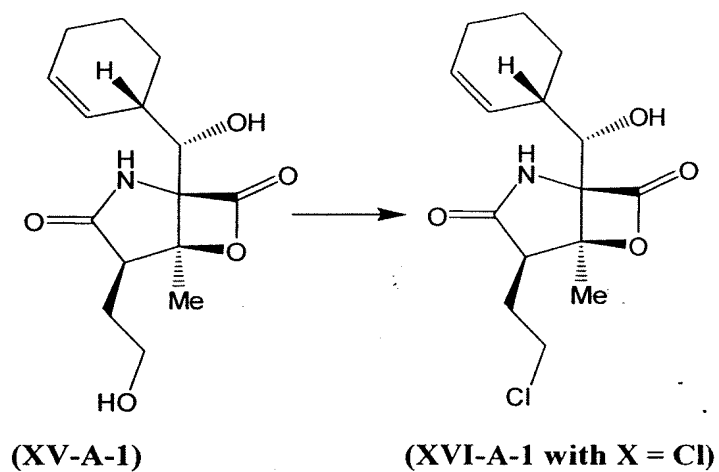


[0186] Examples of the structures and stereochemistry of compounds of formulae (XV) and (XVI) are shown below:

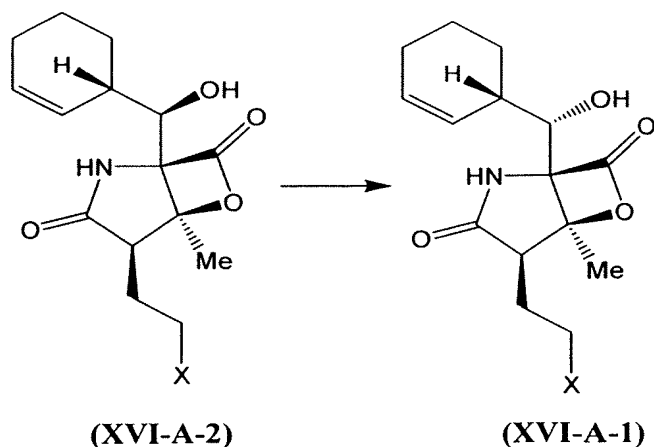




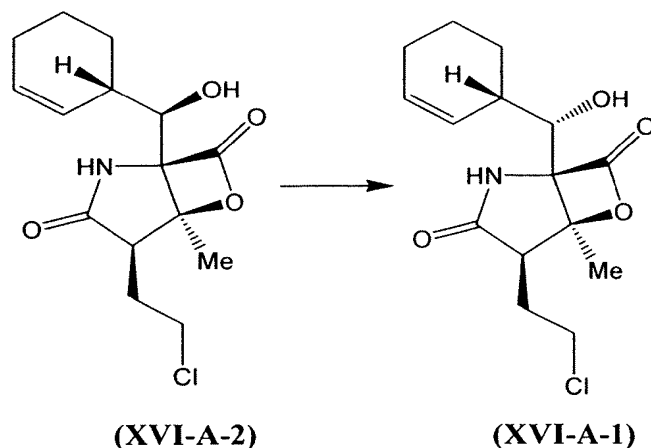
[0187] In one embodiment, Salinosporamide A can be synthesized by chlorinating a compound of formula (XV).



[0188] The stereochemistry of the secondary hydroxy group of the compound of formula (XVI-A-2) can be inverted (e.g., by a Mitsunobu transformation) to form a compound of formula (XVI-A-1).



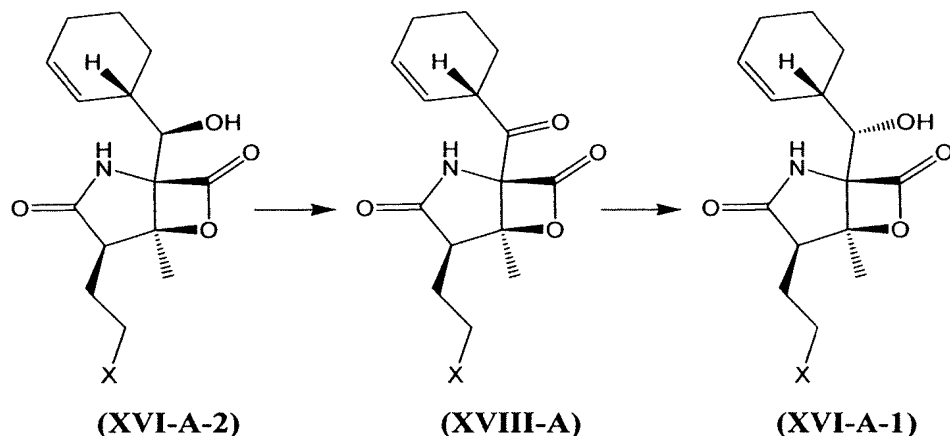
[0189] In one embodiment, Salinosporamide A can be synthesized from a compound with the structure and stereochemistry of formula (XVI-A-2), in which X is Cl, as shown below:



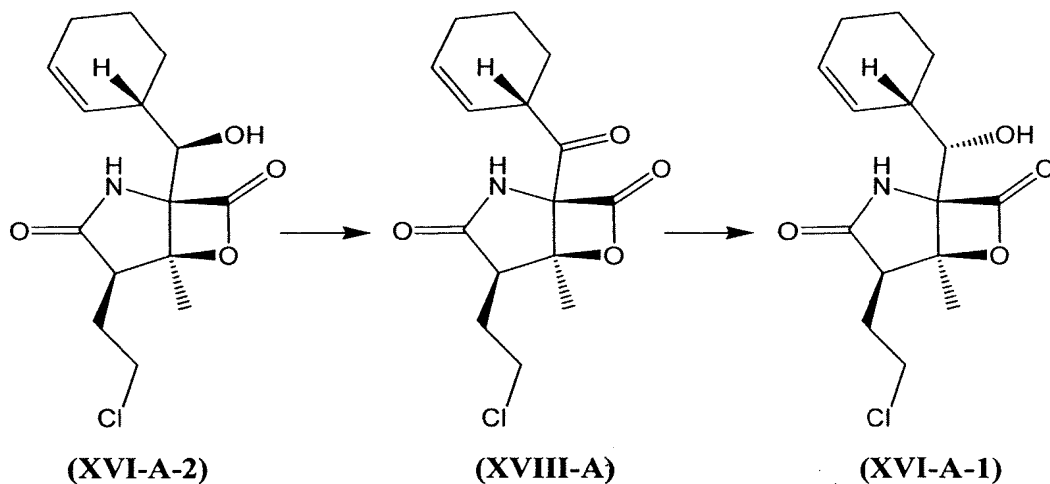
[0190] Alternatively, the stereochemistry of the secondary hydroxy can be inverted via a multistep process, for example, by oxidizing the secondary hydroxy to a ketone and then reducing the ketone to a secondary hydroxy of opposite stereochemistry, as shown in Scheme 13. In one method, the compound of formula (XVI-A-2) can be oxidized with a suitable oxidizing agent (e.g., Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, or PDC) to form the compound of formula (XVIII). The compound of formula (XVIII) can then be reduced to a compound of formula (XVI-A-1)

using a suitable chemical reagent such as sodium borohydride. In some embodiments, the reduction can be accomplished via selective enzymatic transformation. In an embodiment, the reducing enzyme is a ketoreductase such as KRED-EXP-C1A and/or KRED-EXP-B1Y.

Scheme 13



[0191] In another embodiment, Salinosporamide A can be synthesized from a compound with the structure and stereochemistry of formula (XVI-A-2), in which X is Cl, as follows:

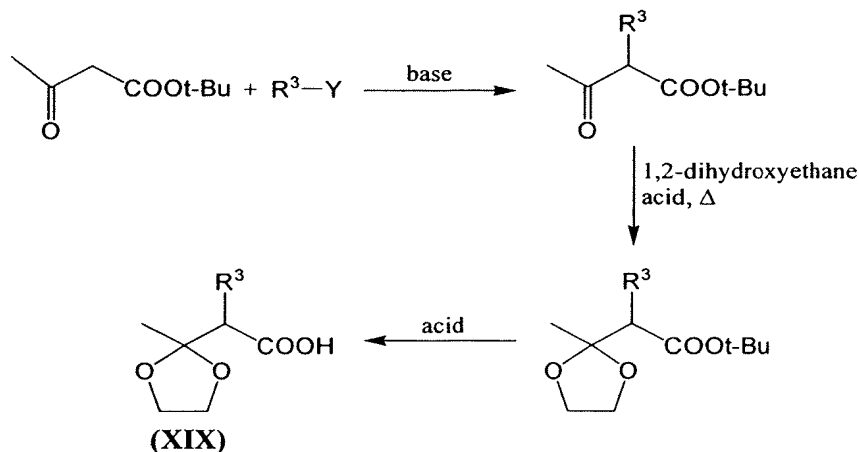


[0192] Moreover, the stereochemistry of the C-5 secondary hydroxy can be inverted at any time after the addition of the cyclohexenyl group to a compound of formula (XIII). For example, the stereochemistry of the secondary hydroxy can be inverted in the compounds of formulae (XIV), (XV) or (XVII). In an embodiment, the stereochemistry of the secondary hydroxy can be inverted in a one step process as

described herein (e.g., by a Mitsunobu transformation). The inversion can also take place in multistep process. Methods for inverting the stereochemistry of C-5 are disclosed herein.

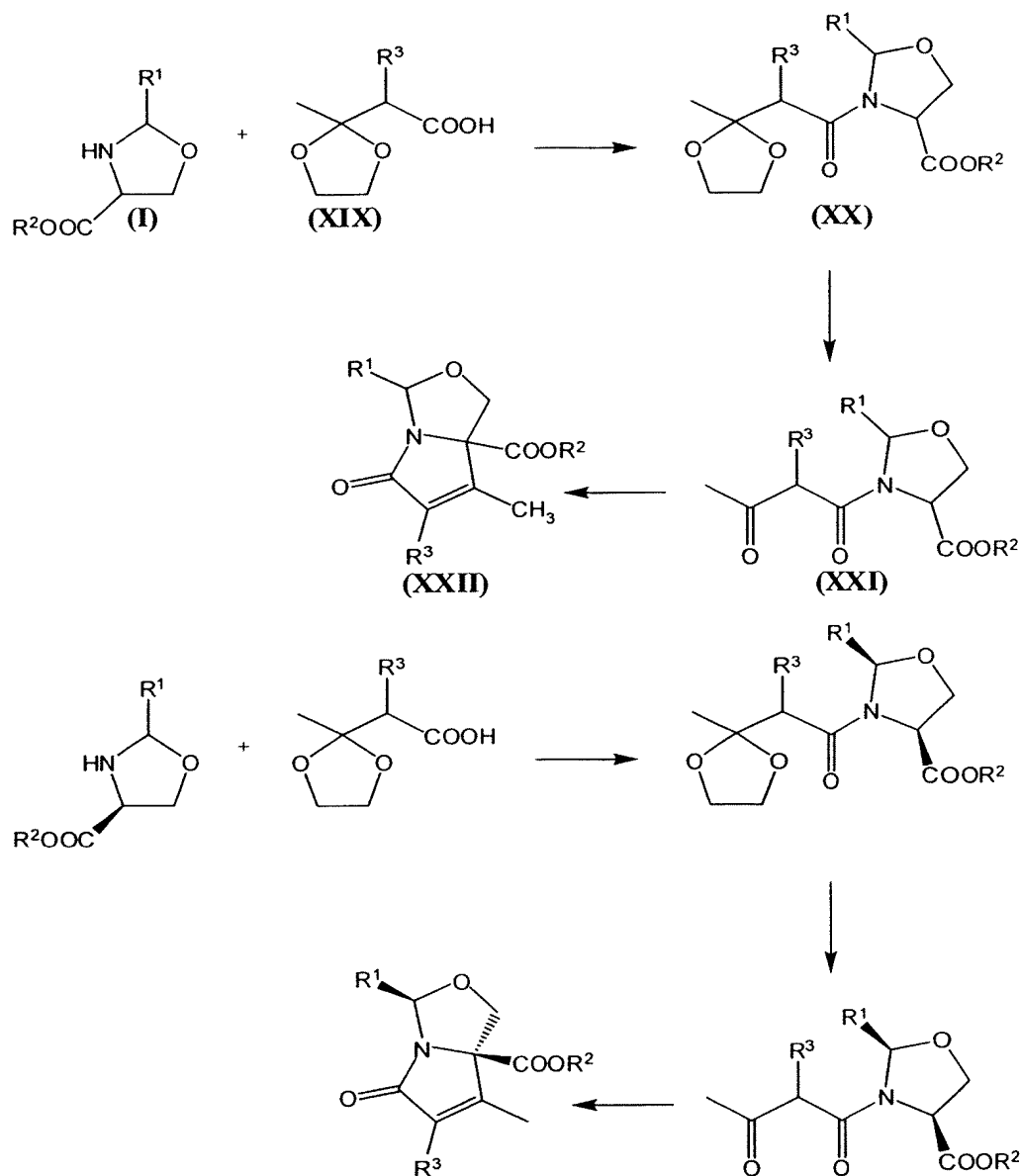
[0193] Salinosporamide A and additional analogs thereof can be synthesized using one or more of the methods shown in Schemes 14-20. In Schemes 14-20, R¹ and R² can be any of the substituents described previously herein.

Scheme 14



[0194] As shown in Scheme 14, analogs of a compound of formula (II) can be obtained in a similar manner as shown in Schemes 2-4 by replacing allylbromide with a compound having the structure R³-Y, wherein Y can be an appropriate leaving group; and R³ can be selected from an unsubstituted or substituted C₁₋₂₄ alkyl, an unsubstituted or substituted C₁₋₂₄ alkenyl, an unsubstituted or substituted C₁₋₂₄ alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C₃₋₂₄ cycloalkyl, an unsubstituted or substituted C₃₋₂₄ cycloalkenyl, an unsubstituted or substituted C₃₋₂₄ cycloalkynyl, an unsubstituted or substituted aryl(C₁₋₆ alkyl) and an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl). In some embodiments, R³ can be a substituted C₁₋₂₄ alkyl. In an embodiment, the substituted C₁₋₂₄ alkyl may be substituted with a halogen, triflate, allylsulfonyl, arylsulfonyl, heteroarylsulfonyl, allylsulfonyloxy, arylsulfonyloxy and heteroarylsulfonyloxy. As to the leaving group denoted by Y, in some embodiments, Y can be halogen or triflate.

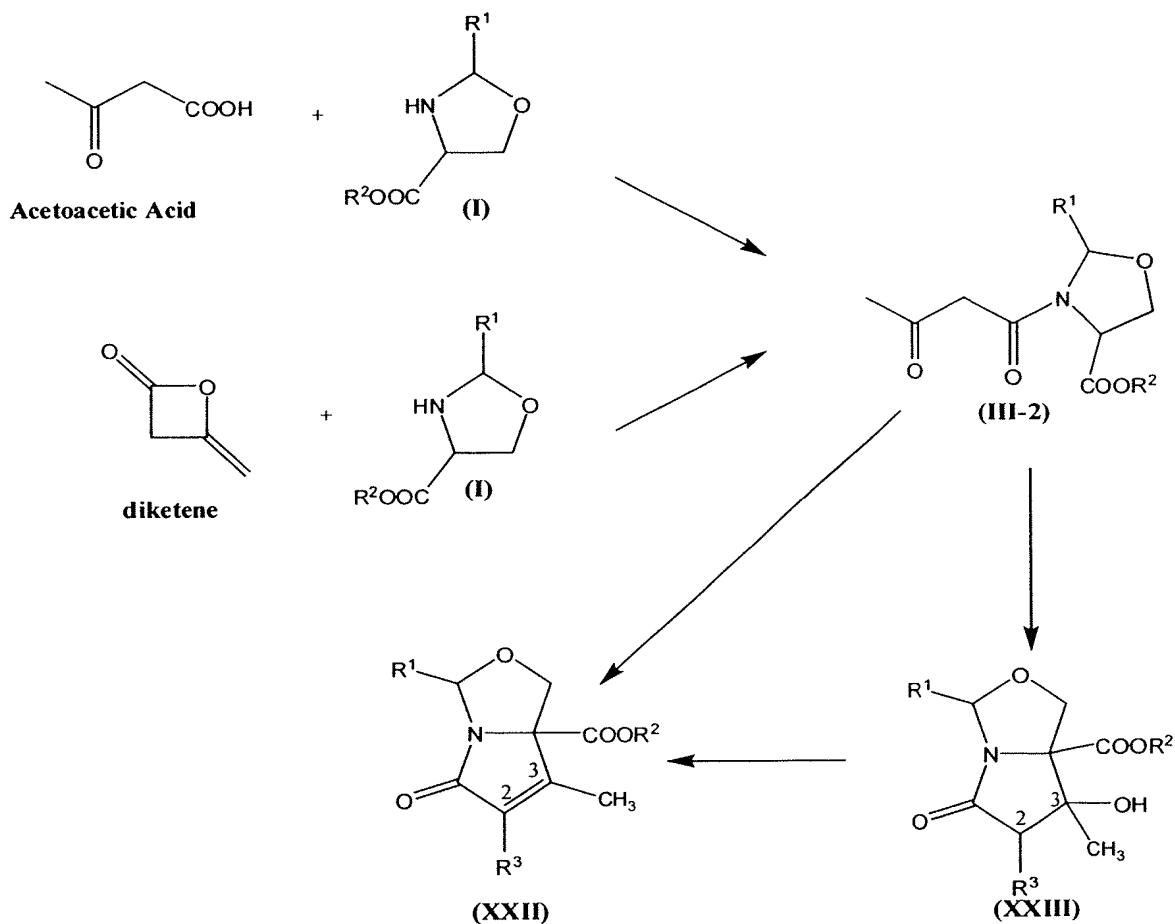
Scheme 15

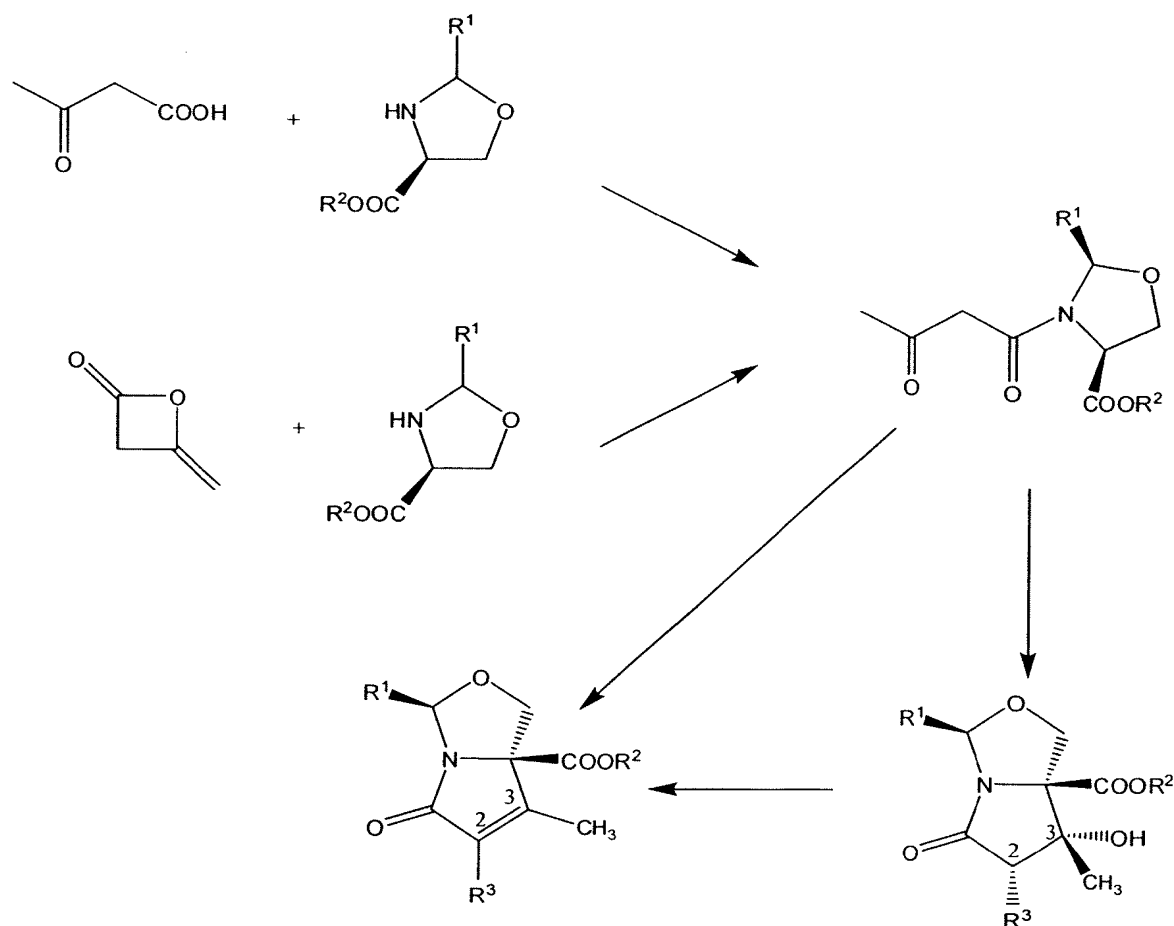


[0195] A compound of formula (XIX) can be reacted with a compound of formula (I) to form a compound of formula (XX) using conditions similar for obtaining a compound of formula (III-1). The compound of formula (XX) can be deprotected to form a compound of formula (XXI). Methods for removing the acetyl protecting group are known to those skilled in the art. For example, suitable methods are described herein, such as those described for obtaining a compound of formula (IV) from a compound of formula (III-1).

[0196] A compound of formula (XXII) can be synthesized from a compound of formula (XXI) using methods known to those skilled in the art. In some embodiments, a compound of formula (XXI) can be treated with an appropriate base to bring about an intramolecular aldol condensation reaction and give a compound of formula (XXII). Examples of the structure and stereochemistry of compounds of formulae (I), (XIX), (XX), (XXI) and (XXII) are shown in Scheme 15.

Scheme 16

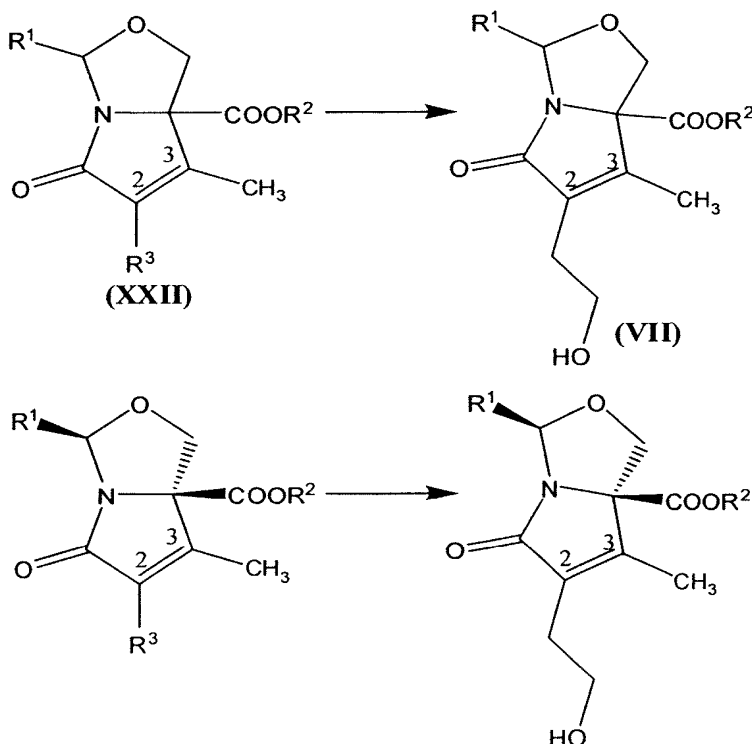




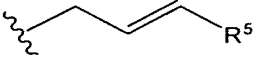
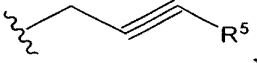
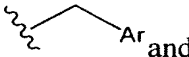
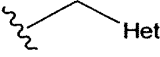
[0197] A compound of formula (XXII) can also be obtained following the transformations shown in Scheme 16. Using the aforementioned conditions and starting with acetoacetic acid and a compound of formula (I) or diketene and a compound of formula (I), a compound of formula (III-2) can be obtained. A compound of formula (XXIII) can be obtained from a compound of formula (III-2) and R³-Y via an alkylation reaction and an intramolecular aldol reaction. As previously discussed, the intramolecular aldol reaction can be induced using an appropriate base, such as those described herein with respect to the synthesis of a compound of formula (V). A compound of formula (XXIII) can then be converted to a compound of formula (XXII). A double bond can be formed between C-2 and C-3 by dehydrating a compound of formula (XXIII) using an appropriate base. Appropriate bases are known to those skilled in the art. For example, an amidine base such as DBU and DBN. Alternatively, in some embodiments, a compound of formula (XXII) can be obtained by reacting a compound of formula (III-2),

R^3 -Y and a base. The compound of formula (XXII) can be synthesized from the aforementioned reagents, in the presence of a base, via an intramolecular aldol reaction and alkylation reaction. As described previously, allyl bromide (an alkylating reagent), and an amidine compound (base) can be used for obtaining a compound of formula (XXII) from a compound of formula (III-2). Also shown in Scheme 16 are examples of the structures and stereochemistry of compounds of formulae (I), (XXII) and (XXIII).

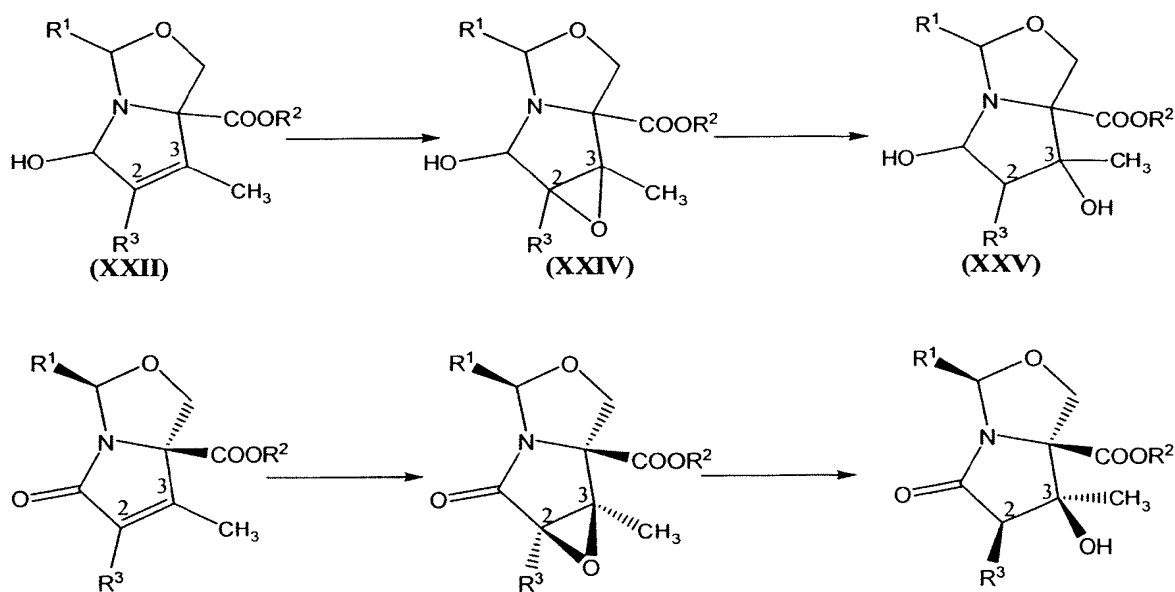
Scheme 17



[0198] A compound of formula (XXII) can be used to obtain a compound of formula (VII). In some embodiments, a compound of formula (VII) can be synthesized from a compound of formula (XXII) via oxidation/reduction methodology. For example, the double, triple bond or aromatic ring included in a R^3 group of a compound of formula (XXII) may be oxidized to an aldehyde using an appropriate oxidizing agent (e.g., ozone, osmium tetroxide and sodium periodate). The aldehyde can be reduced to an alcohol to give a compound of formula (VII) using an appropriate reducing agent such as NaBH_4 , LiAlH_4 or diisobutylaluminum hydride (DIBALH). In some embodiments, R^3 can be

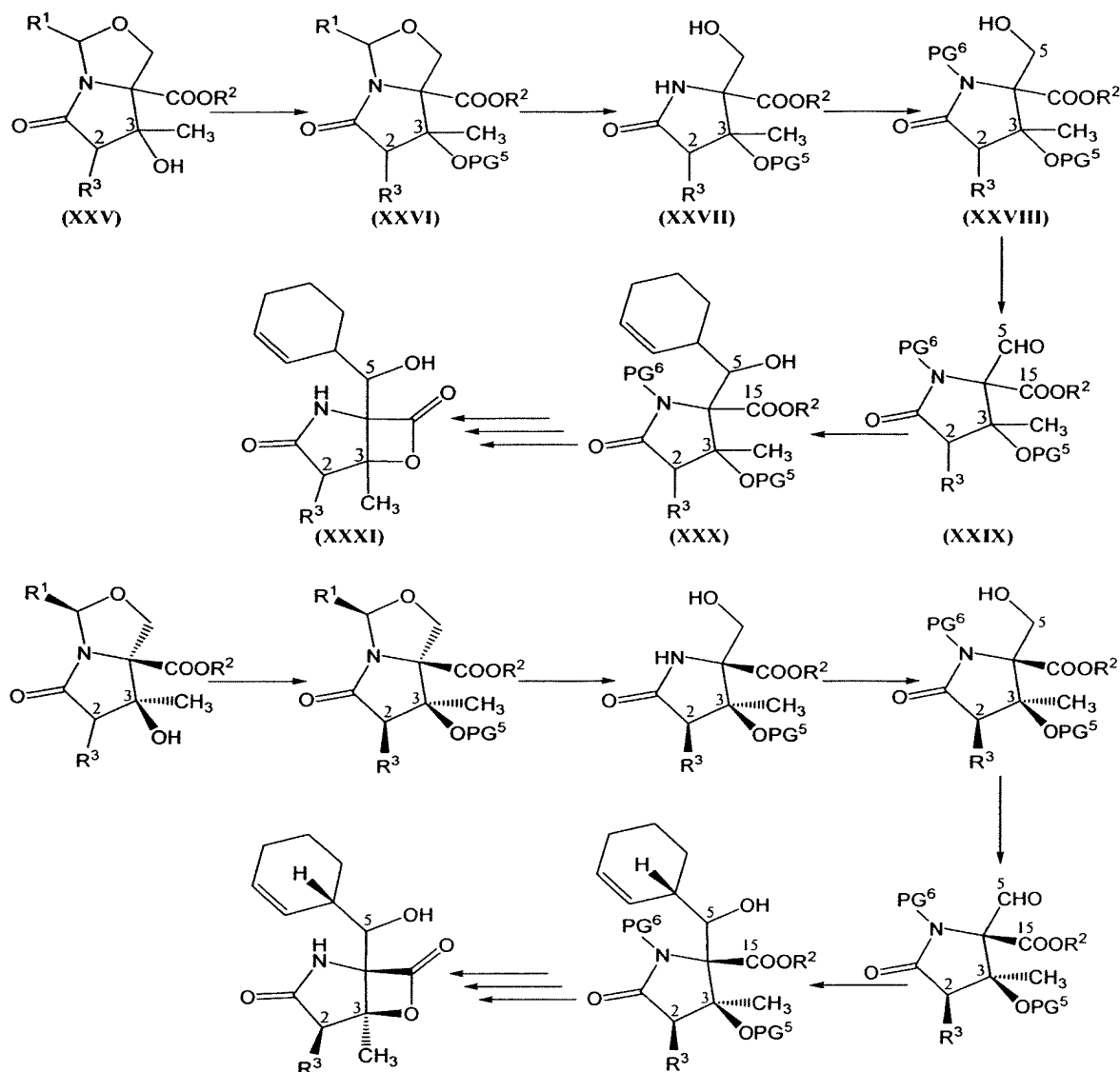
selected from one of the followings: , ,  and , wherein Ar can be an unsubstituted or substituted aryl, Het can be an unsubstituted or substituted heteroaryl; and R⁵ denotes hydrogen or any one of the substituents listed under the definition of substituted. In some embodiments, R⁵ can be selected from hydrogen, an unsubstituted or substituted C₁₋₂₄ alkyl, an unsubstituted or substituted C₁₋₂₄ alkenyl, an unsubstituted or substituted C₁₋₂₄ alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C₃₋₂₄ cycloalkyl, an unsubstituted or substituted C₃₋₂₄ cycloalkenyl, an unsubstituted or substituted C₃₋₂₄ cycloalkynyl, an unsubstituted or substituted aryl(C₁₋₆ alkyl) and an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl). In an embodiment, R⁵ can be hydrogen. In some embodiments, R³ can be a substituted C₁₋₂₄ alkyl. In an embodiment, the substituted C₁₋₂₄ alkyl may be substituted with a halogen, triflate, allylsulfonyl, arylsulfonyl, heteroarylsulfonyl, allylsulfonyloxy, arylsulfonyloxy and heteroarylsulfonyloxy. The compound of formula (VII) obtained from a compound of formula (XXII) can be used to synthesize compounds of formulae (VIII), (IX), (X-1), (X-2), (X-3), (XI-1), (XI-2), (XI-3), (XII-1), (XII-2), (XII-3), (XIII-1), (XIII-2), (XIII-3), (XIV-1), (XIV-2), (XIV-3), (XVII), (XVIII), (XV) and (XVI) using the methodologies described herein, such as those described with respect to Schemes 8, 9, 10, 11, 12 and 13.

Scheme 18



[0199] A compound of formula (XXII) can also be used to form a compound of formula (XXIV). The epoxide of the compound of formula (XXIV) can be synthesized in a similar manner as the epoxide of formula (VIII). In some embodiments, a compound of formula (XXII) can be oxidized to form an epoxide that includes C-2 and C-3. In an embodiment, formation of the epoxide establishes an (*R*)-stereocenter at C-2 and an (*R*)-stereocenter at C-3. Formation of the epoxide stereospecifically can facilitate in establishing the desired stereochemistry in the final compound. The epoxide ring of a compound of formula (XXIV) can be cleaved using one or more suitable reagents, such as a reducing agent. In an embodiment, cleavage of the epoxides establishes an (*R*)-stereocenter at C-2 and an (*S*)-stereocenter at C-3. By establishing the desired chirality at C-2 and C-3, additional steps that may be needed to generate the desired stereochemistry and C-2 and/or C-3 may be averted. Examples of the structures and stereochemistries of compounds of formulae (XXII), (XXIV) and (XXV) are also shown in Scheme 18.

Scheme 19

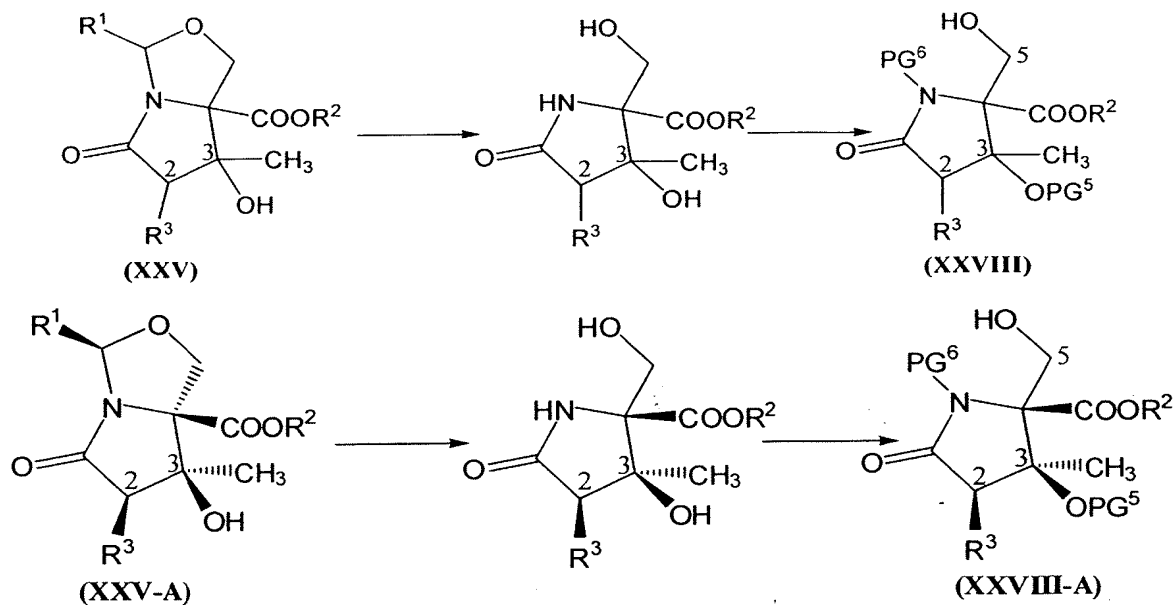


[0200] As shown in Scheme 19, the tertiary hydroxy of a compound of formula (XXV) can be protected with a protecting group moiety, PG⁵ to form a compound of formula (XXVI). Examples of protecting groups that can be used include, but are not limited to, the following: substituted or unsubstituted arylcarbonyls (e.g., benzoyl); substituted or unsubstituted alkylcarbonyls (e.g. acetyl); substituted or unsubstituted arylalkylcarbonyls; substituted or unsubstituted alkoxycarbonyls; substituted or unsubstituted aryloxy carbonyls; substituted methyl ether (e.g. methoxymethyl); substituted ethyl ether; substituted or substituted benzyl (e.g. benzyl, 4-methoxybenzyl);

tetrahydropyranyl ether; silyl ethers (e.g., trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyltrimethylsilyl, or t-butylphenylsilyl); esters, carbonates (e.g. methoxymethylcarbonate); and sulfonates (e.g. mesylate, tosylate).

[0201] The amination of a compound of (XXVI) can be cleaved using an acid to form a compound of formula (XXVII). Examples of suitable acids include, but are not limited to, triflic acid, HCl, PTSA, PPTS, TFA and/or camphor sulfonic acid. As discussed herein, the lactam nitrogen may be protected with a protecting group, PG⁶, to form a compound of formula (XXVIII). Examples of suitable protecting groups are described herein. In some embodiments, PG⁶ can be a benzyl, a substituted benzyl, a silyl or methoxymethyl. In an embodiment, the lactam nitrogen is protected so that the 2-cyclohexenyl ring will add to C-5 to form an (*S*)-stereocenter. As previously discussed, the protection of the lactam nitrogen can also aid in establishing an (*S*)-stereocenter at C-6. Alternatively, the tertiary hydroxy group on C-3 can be protected after cleavage of the amination. For example, the tertiary hydroxy group can remain unprotected and the amination can be cleaved as described herein. After cleavage of the amination, a suitable protecting group, such as those described herein, can be used to protect the tertiary hydroxy group on C-3 and form a compound of formula (XXVIII).

Scheme 19a

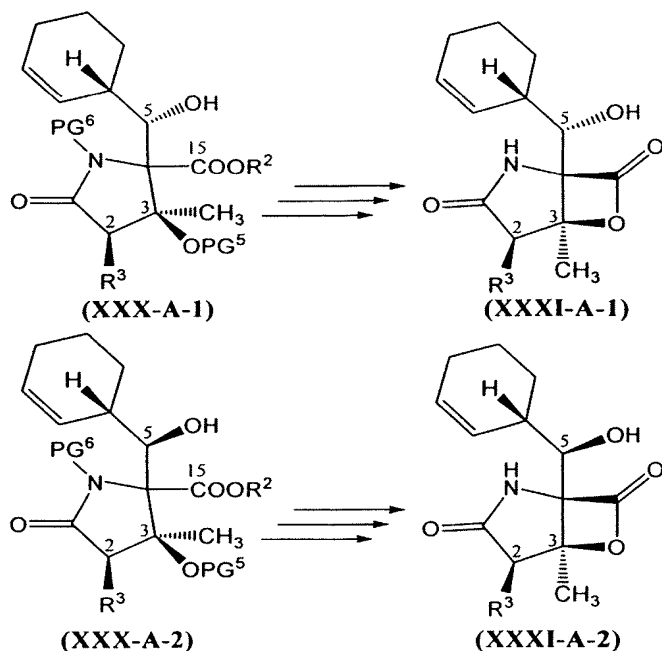


[0202] The primary alcohol at C-5 can be oxidized to form a compound of formula (XXIX). A non-limiting list of oxidizing agents include Dess-Martin periodinane, TPAP/NMO, Swern oxidation reagent, PCC, or PDC. A cyclohexenyl ring can be added to C-5 position of a compound of formula (XXIX) to form a compound of formula (XXX). Methods for adding the cyclohexenyl ring are known to those skilled in the art. In some embodiments, the cyclohexenyl ring can be added via an alkylation reaction. In an embodiment, the alkylation reaction utilizes an organometallic moiety. Suitable organometallic moieties are described herein. In an embodiment, the organometallic moiety can be an organomagnesium compound.

[0203] The protecting groups, if present, can be removed using methods known to those skilled in the art, and a 4-membered heterocyclic ring can be formed using suitable methodologies to give a compound of formula (XXXI). As an example, the beta-lactone can be formed using an appropriate base (e.g., BOPCl/pyridine, triethylamine) to induce lactonization. In an embodiment, the C-15 ester can first be transformed to a carboxylic acid, an activated acid (e.g., acid halide), or an activated ester (e.g., p-nitrophenyl ester, pentafluorophenyl ester, pentafluoroethyl ester, trifluoroethyl ester, trichloroethyl ester, a thioester, etc.) before being treated with an appropriate reagent to induce the lactonization reaction. In an embodiment, the C-15 carboxylic acid can be treated with an appropriate base to affect the lactonization reaction. Also shown in Scheme 19 are examples of structures and stereochemistries of compounds of formulae (XXV), (XXVI), (XXVII), (XXVIII), (XXIX), (XXX) and (XXXI). Additional examples of structures and stereochemistries of compounds (XXX) and (XXXI) are shown below in Scheme 20.

[0204] If the tertiary hydroxy is not protected, a compound of formula (XXXI) can still be obtained using the conditions and reagents described above. Likewise, if the lactam nitrogen is not protected, the conditions and reagents described above can also be used to obtain a compound of formula (XXXI). Removal of PG⁵ and PG⁶ can occur at any suitable point in the synthesis of a compound of formula (XXXI). For example, the lactam nitrogen protecting group can be removed anytime after the addition of the cyclohexenyl ring. Similarly, the tertiary hydroxy protecting group, PG⁶, can be removed anytime before the formation of the 4-membered heterocyclic ring.

Scheme 20

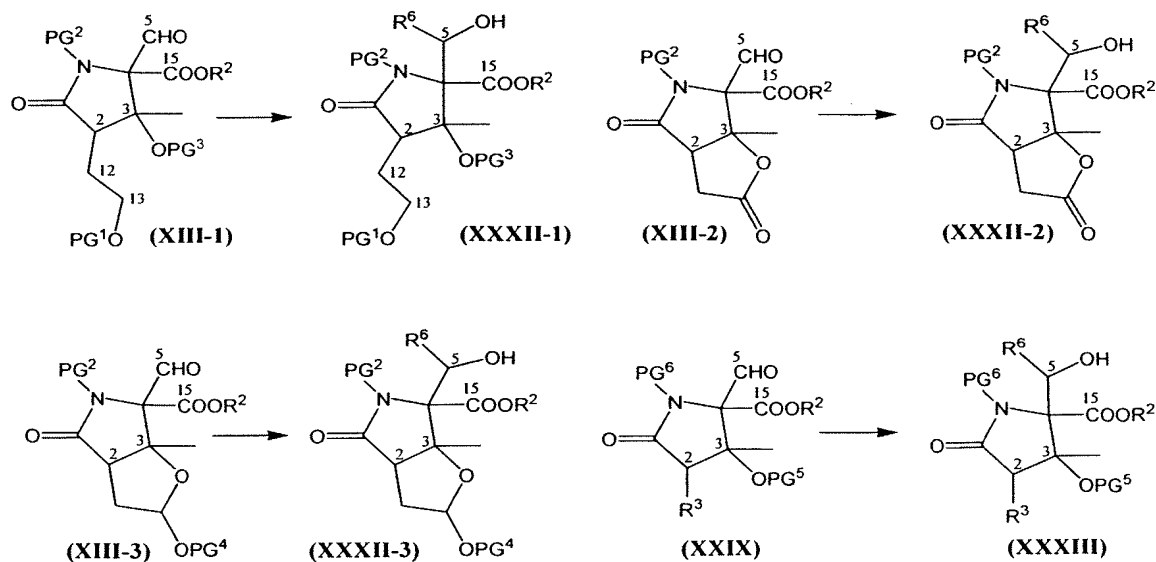


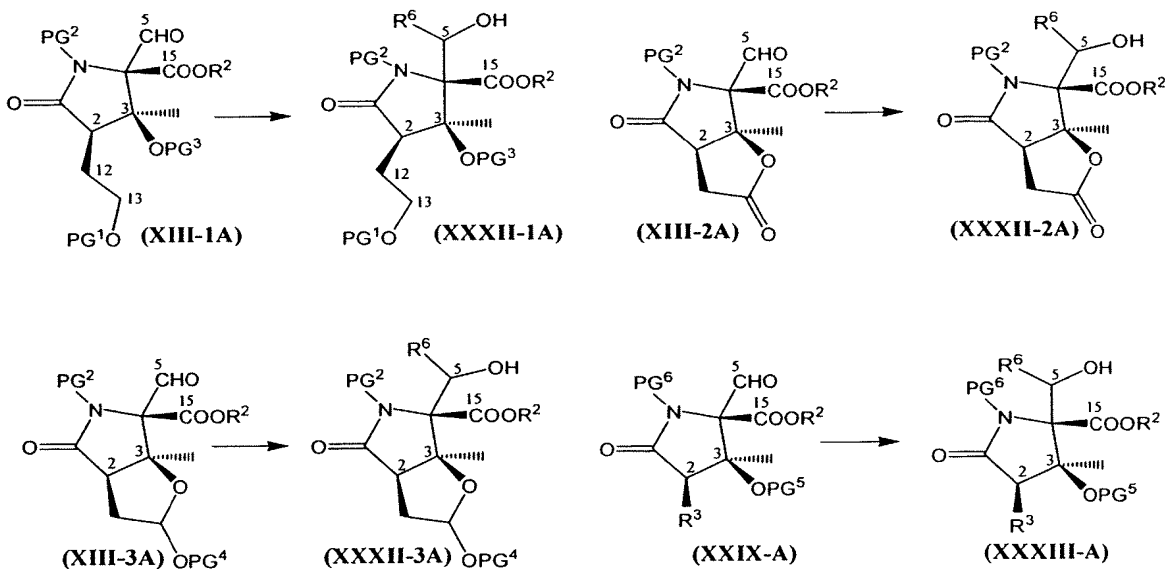
[0205] If C-5 is an (*R*)-stereocenter, the stereocenter can be inverted to an (*S*)-stereocenter using a method described herein. For example, the chirality of C-5 can be inverted using a one step or multistep process such as those described herein.

[0206] Instead of adding 2-cyclohexenyl, various substituents can be utilized to form analogs of Salinosporamide A. As shown in Scheme 21, R⁶ can be added to a compound of formula (XIII-1), (XIII-2), (XIII-3) or (XXIX-1), wherein R⁶ can be selected from an unsubstituted or substituted C₁-C₂₄ alkyl, an unsubstituted or substituted C₂-C₂₄ alkenyl, an unsubstituted or substituted C₂-C₂₄ alkynyl, an unsubstituted or substituted C₃-C₂₄ cycloalkyl, an unsubstituted or substituted C₃-C₂₄ cycloalkenyl, an unsubstituted or substituted C₃-C₂₄ cycloalkynyl, an unsubstituted or substituted heterocyclyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted aryl(C₁₋₆ alkyl), an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl), an unsubstituted or substituted C₃-C₂₄ cycloalkyl(C₁₋₆ alkyl) and an unsubstituted or substituted heterocyclyl(C₁₋₆ alkyl); and wherein R³, R², PG¹, PG², PG³, PG⁴, PG⁵ and PG⁶ have been previously defined herein. In some embodiments, R⁶ can be selected from an unsubstituted or substituted C₁-C₁₂ alkyl, an unsubstituted or substituted C₂-C₁₂ alkenyl, an unsubstituted or substituted C₂-C₁₂ alkynyl, an unsubstituted or

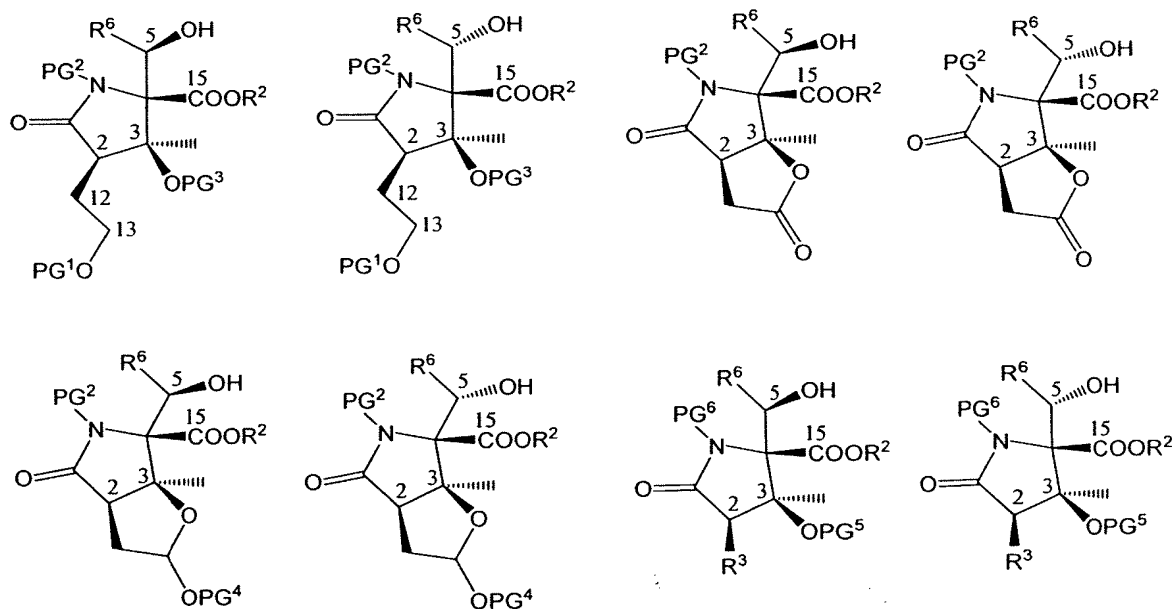
substituted C₃-C₁₂ cycloalkyl, an unsubstituted or substituted C₃-C₁₂ cycloalkenyl, an unsubstituted or substituted C₃-C₁₂ cycloalkynyl, an unsubstituted or substituted heterocyclyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted aryl(C₁₋₆ alkyl), an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl), an unsubstituted or substituted C₃-C₁₂ cycloalkyl(C₁₋₆ alkyl) and an unsubstituted or substituted heterocyclyl(C₁₋₆ alkyl). In an embodiment, R⁶ can be a C₁₋₂₄ alkyl. In an embodiment, the C₁₋₂₄ alkyl can be isopropyl. Examples of the structures and stereochemistries of compounds of formulae (XIII-1), (XIII-2), (XIII-3) and (XXIX-1), and their respective products after addition of R⁶, compounds of formulae (XXXII-1), (XXXII-2), (XXXII-3) and (XXXIII), respectively, are also shown in Scheme 21.

Scheme 21





[0207] Additional examples of the structure and stereochemistries of compounds of formulae (XXXII-1), (XXXII-2), (XXXII-3) and (XXXIII) are shown below.

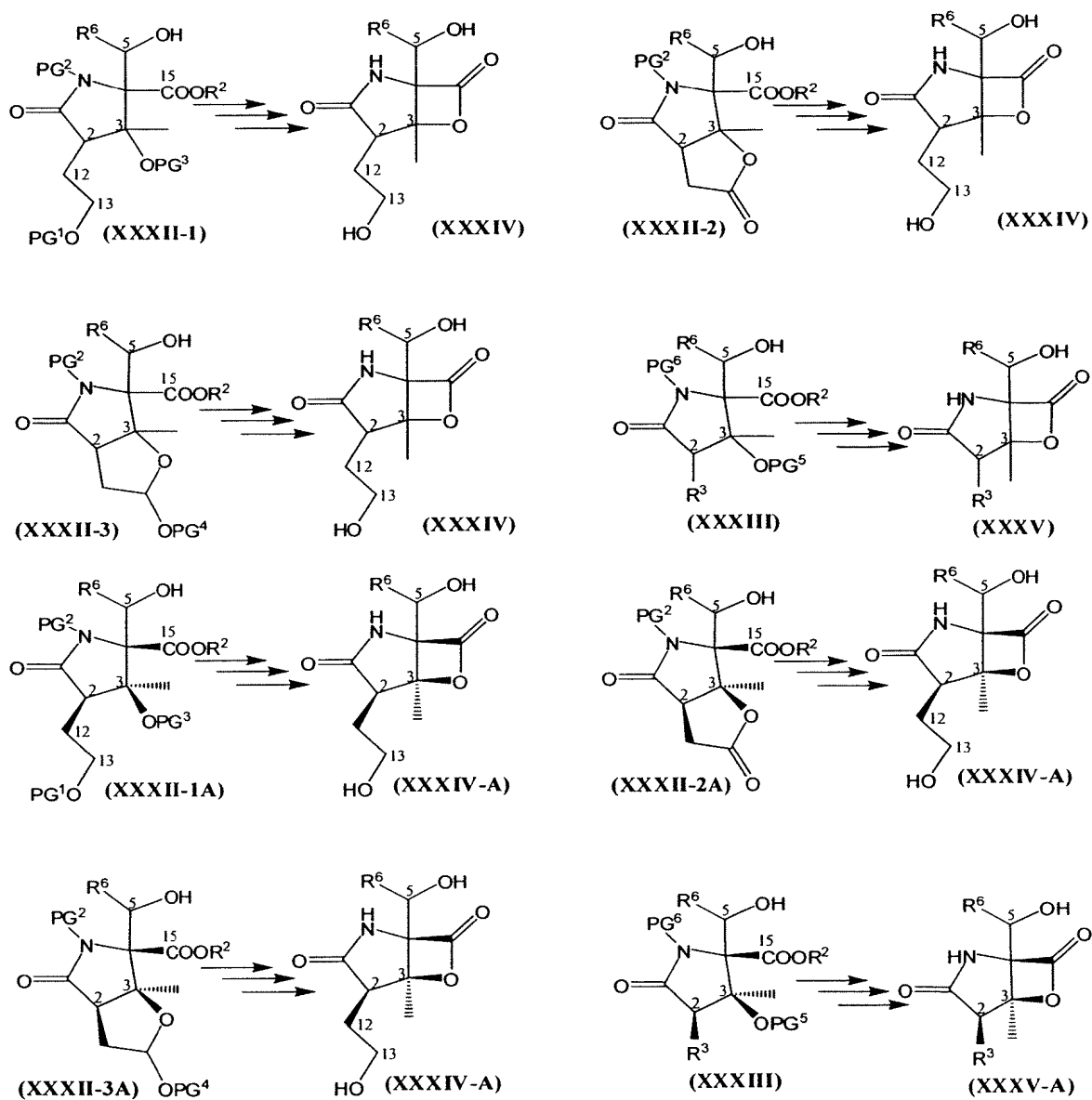


[0208] A variety of methods are known to those skilled in the art for adding a R⁶ moiety to compounds of formulae (XIII-1), (XIII-2), (XIII-3) and (XXIX-1). In some embodiments, R⁶ can be added using an organometallic moiety such as those described herein. A non-limiting list of suitable organometallic moieties include organomagnesium

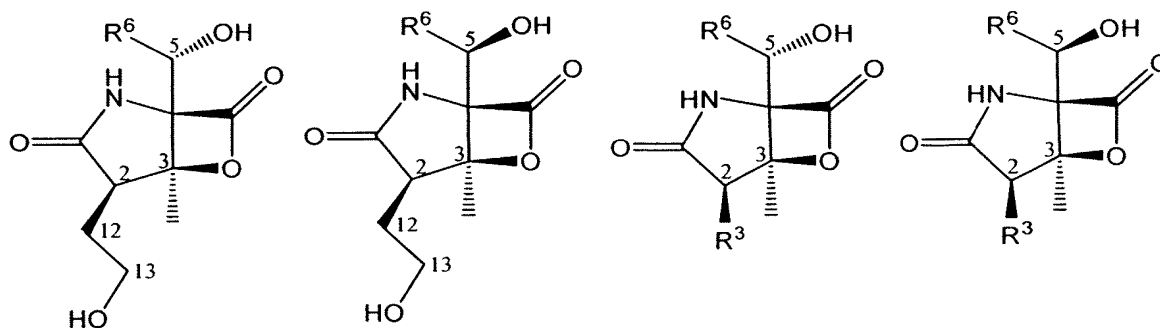
compounds, organolithium compounds, organotin compounds, organocuprates compounds, organozinc, and organopalladium compounds, metal carbonyls, metallocenes, carbene complexes, and organometalloids (e.g., organoboranes and organosilanes). In some embodiments, the organometallic moiety can be selected from $R^6\text{-MgR}^7$, $R^6\text{-ZnR}^7$, $R^6\text{-Li}$, $(R^6)_s\text{-B(R}^7\text{)}_{3-s}$, and $(R^6)_t\text{-Sn(R}^7\text{)}_{4-t}$; wherein R^7 can be selected from halogen, or substituted or unsubstituted variants of the following: alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, isopinocampheyl, hydroxy, alkoxy, and carbonylalkoxy, wherein if more than one R^7 is present, the R^7 groups can optionally be bonded together to form an optionally substituted cycloalkyl (e.g., 9-BBN), optionally substituted cycloalkenyl, optionally substituted heteroalkyl or optionally substituted heteroalkenyl ring; s can be an integer from 1 to 3; and t can be an integer from 1 to 4.

[0209] After addition of R^6 , compounds of formulae (XXXII-1), (XXXII-2), (XXXII-3) and (XXXIII) can be used to form analogs of Salinosporamide A via the methodologies discussed with respect to Schemes 9, 10, 11, 12, 13 and 19. For example, any protecting groups on compounds of formulae (XXXII-1), (XXXII-2), (XXXII-3) and (XXXIII) can be removed in any suitable order, and a 4-membered heterocyclic ring can be formed using methods known to those skilled in the art, including those described herein. The resulting compounds such as compounds of formulae (XXXIV) and (XXXV) can have the structures and stereochemistries shown in Scheme 22. If desired or needed, the chirality of C-5 can be inverted using one or methods described herein. As discussed previously, any protecting groups present on compounds of formulae (XIII-1), (XIII-2), (XIII-3) and (XXIX-1) can be removed at anytime. Additionally, the stereochemistry of the C-5 secondary hydroxy can be inverted at any time after the addition of the R^6 group to compounds of formulae (XIII-1), (XIII-2), (XIII-3) and (XXIX-1).

Scheme 22

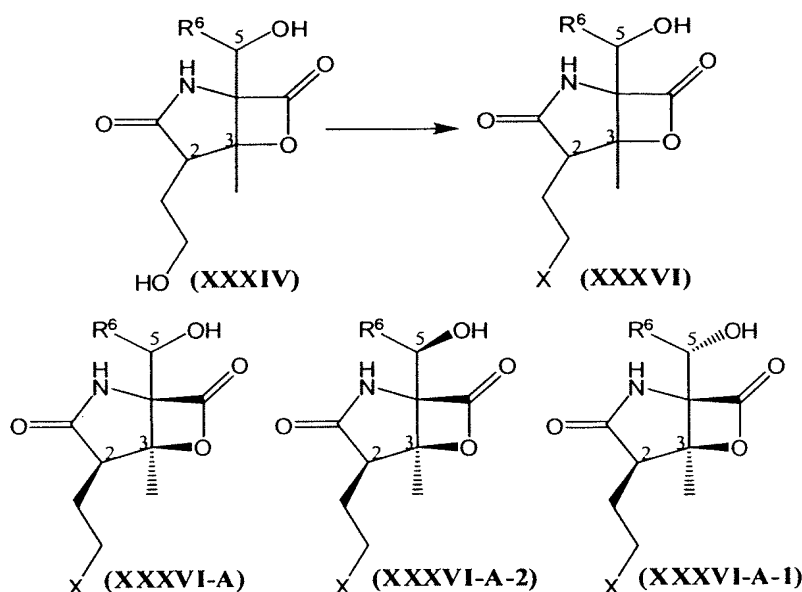


[0210] Additional examples of the structure and stereochemistries of compounds of formulae (XXXIV) and (XXXV) are shown below.



[0211] As shown in Scheme 23, additional analogs of Salinsporamide A can be obtained by replacing the hydroxy group attached to C-13. Examples of the structures and stereochemistries of compounds of formulae (XXXIV) and (XXXVI), in which R^6 and X have been previously defined herein, are shown below.

Scheme 23

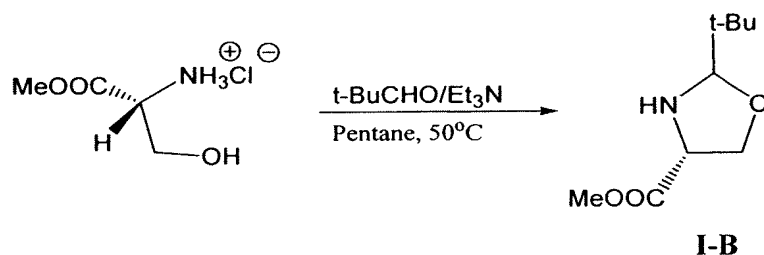


[0212] Additional information regarding the conditions and reagents that can be used are disclosed in U.S. Patent No., 7,183,417, issued February 27, 2007; U.S. Application Serial Nos. 11/697,689, filed April 6, 2007, and 11/434,698, filed May 16, 2006; International Application No. PCT/US2005/012113, filed April 11, 2005 and the following articles: Margalef et al. *Tetrahedron* (2008) **64**(34) 7896-7901 and Takahashi et al., *Angew. Chemie, Int. Ed.* (2008) **47**, 1-4.

EXAMPLES

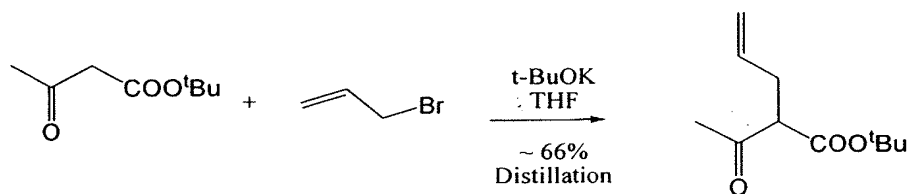
[0213] Embodiments are disclosed in further detail in the following examples, which are not in any way intended to limit the scope of the claims.

EXAMPLE 1
SYNTHESIS OF (I-B) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



[0214] To a suspension of (R)-serine methylester hydrochloride (25 g, 160.67 mmol) in pentane (800 mL) at room temperature were added t-butyl aldehyde (20.73 g, 241 mmol) and Et_3N (17.85 g, 176.74 mmol). The reaction mixture was refluxed for 15 hrs at 50 °C using Dean-Stark apparatus. The resulting reaction mixture was cooled to room temperature, filtered through celite, and the celite cake was washed with pentane (2 X 40 mL). The combined filtrate was concentrated under reduced pressure and dried under high vacuum to afford product, **I-B** (24.5 g, 131 mmol, 81.5% yield) as clear oil, which can be used without further purification. The compound **I-B** was characterized by $^1\text{H-NMR}$ (CDCl_3 , 500 MHz). See Figure 7.

EXAMPLE 2
SYNTHESIS OF THE ESTER PRECURSOR OF COMPOUND (II)



Method A

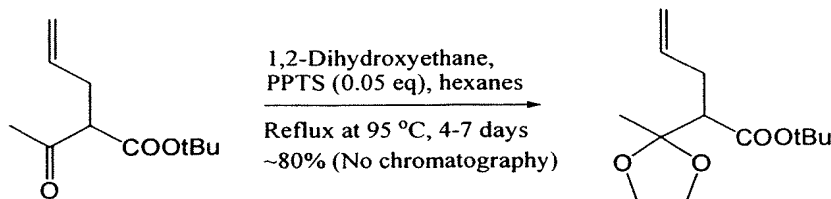
[0215] To a solution of t-butylacetoacetate (30 g, 0.19 mol) in dry THF (800 mL) at 0 °C was added t-BuOK (23.41 g, 95% w/w, 0.21 mol) and the solution was

stirred for about 15 minutes. Allylbromide (18.39 g, 0.152 mol) was added and the solution was stirred at 0 °C for additional 15 min. The reaction mixture was then allowed to warm to room temperature and stirred for about 5 hours under an atmosphere of N₂. The above reaction mixture was then cooled to 0 °C, quenched with H₂O (300 mL), and extracted with EtOAc (3 X 200 mL). The combined organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (5 cm ID X 45 cm) using a solvent gradient of 100% hexanes (1.5 L) to 1.5% EtOAc/hexanes (3 L) to 2.5% EtOAc/hexanes (1 L) to 4% EtOAc/hexanes (700 mL) to afford pure product (14.5g, 0.073 mol, 38.5% yield). Alternatively, the crude product was purified by fractional distillation (130°C oil bath, 90-95°C bp) under high vacuum (12 mm Hg) to afford product, the ester precursor of the compound **II** (66% yield).

Method B

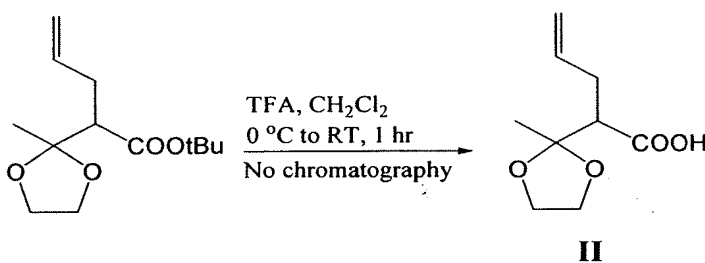
[0216] To a solution of t-BuOK (50g, 95% w/w, 0.42 mol) in dry THF (1.5 L) at 0°C was added t-butylacetoacetate (65 g, 0.41 mol) and the solution was stirred for about 15 minutes under an atmosphere of N₂. Allylbromide (47g, 0.39mol) was added slowly and the solution was stirred at 0 °C for about 20 hours. The reaction mixture was allowed to warm to room temperature and stirred for additional 15 hours. The reaction mixture was then quenched with H₂O (1L) at 0 °C and extracted with EtOAc (3 X 0.5 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by fractional distillation (130 °C oil bath, 90-95 °C bp) under high vacuum (12 mm Hg) to afford the product, the ester precursor of the compound **II** (54 g, 0.27mol, 66% yield). ¹H-NMR (CDCl₃, 500 MHz) (δ): 5.68 (m, 1H), 5.03 (br dd, *J*=1, 17 Hz, 1H), 4.97 (br dd, *J*= 1, 10 Hz, 1H), 3.35 (t, *J*= 7.5 1H), 2.48 (br t, *J*=7.0, 2H), 2.16 (s, 3H), 1.39 (s, 9H). See Figure 8.

EXAMPLE 3
SYNTHESIS OF THE PROTECTED ESTER PRECURSOR OF COMPOUND (II)



[0217] To a solution of the ester precursor (45 g, 0.23 mol) in hexanes (1.6 L) were added ethylene glycol (70.5 g, 1.15 mol) and PPTS (2.85 g, 0.011 mol). The reaction mixture was refluxed at 95 °C using Dean-Stark apparatus for 6 days (Note: 28.5 g, 0.46 mol of ethylene glycol was added to the reaction mixture every two days to maintain its concentration), then cooled to room temperature. The reaction mixture was then neutralized with 800 μ L of Et₃N and diluted with H₂O (500 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated under reduced pressure to afford product, the protected ester precursor of the compound II (44 g, 0.18 mmol, 80% yield), which can be used for the next step without purification. ¹H-NMR (CDCl₃, 500 MHz) (δ): 5.72 (m, 1H), 5.06 (dd, J =1, 17 Hz, 1H), 4.97 (d, J = 10 Hz, 1H), 3.94 (m, 4H), 2.60 (dd, J =3.6, 11.5 Hz, 1H), 2.43 (m, 1H), 2.29 (m, 1H), 1.42 (s, 9H), 1.38 (s, 3H). See Figure 9.

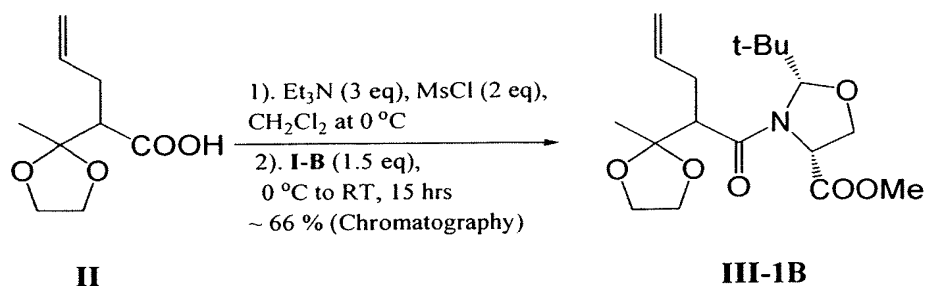
EXAMPLE 4
SYNTHESIS OF COMPOUND (II)



[0218] To a solution of the protected ester precursor (28g, 0.115 mol) in CH₂Cl₂ (28 mL) at 0 °C was added trifluoroacetic acid (TFA neat, 56 mL, 0.727 mol) and the solution was stirred for about 5 min. The reaction mixture was then allowed to warm to room temperature and stirred for one hour. The reaction mixture was diluted with

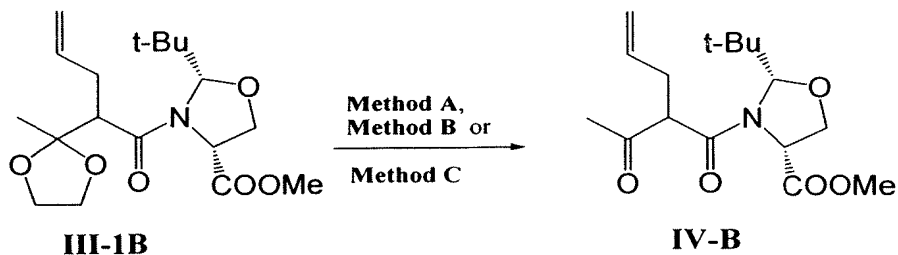
CH₂Cl₂ (400 mL) and extracted with ice cold water (3 X 300 mL). The organic layer was dried over Na₂SO₄, concentrated under reduced pressure and dried under high-vacuum for about one hour (to remove the residual TFA) to afford the product, compound **II** (15.5g, 0.083 mol, 72% yield) as light yellow oil, which can be used for the next step without purification. The compound **II** was characterized by ¹H-NMR (CDCl₃, 500 MHz): ¹H-NMR (CDCl₃, 500 MHz) (δ): 5.77 (m, 1H), 5.10 (br dd, *J*=1, 17 Hz, 1H), 5.02 (br d, *J*= 10 Hz, 1H), 4.00 (m, 4H), 2.76 (dd, *J*=3.8, 11.0 Hz, 1H), 2.43 (m, 2H), 1.41 (s, 3H). See Figure 10.

EXAMPLE 5
SYNTHESIS OF COMPOUND (III-1B) (R¹ = t-BUTYL AND R² = METHYL)



[0219] To a solution of compound **II** (4.8g, 25.81 mmol) in dry CH₂Cl₂ (200 mL) at 0 °C were added Et₃N (7.82g, 77.42 mmol) and methanesulfonyl chloride (5.89g, 51.62 mmol) and the solution was stirred for about 10 min. Then compound **I-B** (5.31g, 28.4 mmol) was added, the reaction mixture was allowed to warm to room temperature slowly and stirred for about 15 hrs. Then the reaction mixture was quenched with H₂O (200 mL) and extracted with CH₂Cl₂ (3 X 100 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to yield **III-1B** as a mixture of two diastereomers (3:2). See Figure 11b. The crude product was purified by silica flash chromatography (3 cm ID X 30 cm) using a solvent gradient of 19:1 (500 mL) to 9:1 (500 mL) to 17:3 (500 mL) to 4:1 (1.5 L) to 3:1 (1 L) hexane/EtOAc to afford the product, compound **III-1B** (6g, 16.9 mmol, 65.5% yield). The compound **III-1B** was characterized by ¹H-NMR (CDCl₃, 500 MHz) and LC-MS. See Figures 11a and 11b. MS (ESI) *m/z* 356 [M+H]⁺.

EXAMPLE 6
SYNTHESIS OF COMPOUND (IV-B) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



[0220] Method A: To a solution of compound **III-1B** (6 g, 16.9 mmol) in CH_3CN (350 mL) were added sodium iodide (3.3 g, 21.97 mmol) and cerium (III) chloride heptahydrate (9.45 g, 25.35 mmol) and the reaction mixture was stirred at 60-65°C for 4 hours (the reaction progress can be monitored by LC-MS). The above reaction mixture was then quenched with water (200 mL) and extracted with EtOAc (3 X 150 mL). The combined organic layer (cloudy) was concentrated under reduced pressure to remove all of the CH_3CN /EtOAc, leaving about 20 mL of H_2O (CH_3CN soluble part), which was further extracted with EtOAc (100 mL). The organic layer was dried over Na_2SO_4 , and concentrated under reduced pressure to afford the product, **IV-B** (4.4 g, 14.2 mmol, 83.5% yield) as a mixture of two diastereomers (3:2). See Figure 12e. If desired, the product can be used for the next step without purification. The compound **IV-B** was characterized by ^1H -NMR (CDCl_3 , 500 MHz) and NOESY (CDCl_3 , 500 MHz). See Figures 12a and 12b. MS (ESI) m/z 312 $[\text{M}+\text{H}]^+$. A portion of the product was further purified by reverse phase HPLC using C-18 column (150 mm X 21 mm), and an isocratic solvent system of 40% acetonitrile in H_2O at a flowrate of 14.5 mL/min to afford individual diastereomers **IV-B1** and **IV-B2** as pure samples. The diastereomers **IV-B1** and **IV-B2** were characterized by ^1H -NMR (CDCl_3 , 500 MHz). See Figures 12c and 12d.

[0221] Compound IV-B1: ^1H -NMR (CDCl_3 , 500 MHz) (δ): 5.73 (m, 1H), 5.34 (s, 1H), 5.12 (m, 1H), 5.05 (d, $J = 10.1$ Hz, 1H), 4.64 (d, $J = 6.3$ Hz, 1H), 4.53 (d, $J = 8.2$ Hz, 1H), 3.90 (t, $J = 7.6$ Hz, 1H), 3.80, (s, 3H), 3.67 (t, $J = 7.6$ Hz, 1H), 2.60 (m, 2H), 2.27 (s, 3H), 0.91 (s, 9H); MS (ESI) m/z 312 $[\text{M}+\text{H}]^+$.

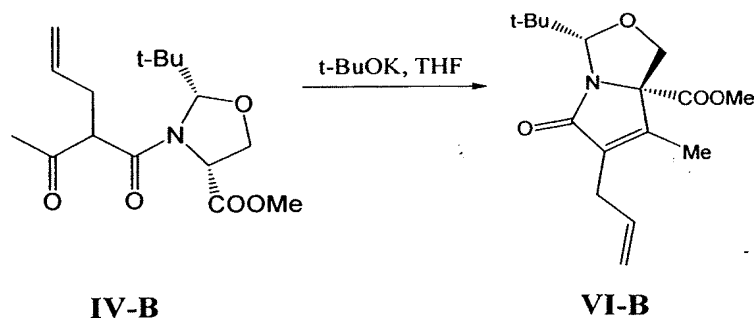
[0222] Compound IV-B2: ^1H -NMR (CDCl_3 , 500 MHz) (δ): 5.76 (m, 1H), 5.28 (s, 1H), 5.18 (br d, $J = 17.3$ Hz 1H), 5.08 (d, $J = 10.1$ Hz, 1H), 4.88 (m, 1H), 4.52 (d,

$J = 8.2$ Hz, 1H), 3.88 (m, 1H), 3.81, (m, 1H), 3.76 (s, 3H), 2.88 (m, 1H), 2.63 (m, 1H), 2.21 (s, 3H), 0.86 (s, 9H); MS (ESI) m/z 312 $[M+H]^+$.

[0223] Method B: A mixture of compound **III-1B** (175 mg, 0.493 mmol) and iodine (12.52 mg, 0.0493 mmol) in acetone (20 mL) was refluxed at 56 °C for one hour. The reaction mixture was then cooled to RT, the acetone was removed under reduced pressure, and the crude reaction product was dissolved in CH_2Cl_2 (20 mL). The CH_2Cl_2 solution was washed successively with 5% aqueous sodium thiosulfate (10 mL), H_2O (10 mL) and brine (10 mL). The resulting organic phase was dried over Na_2SO_4 , concentrated under reduced pressure and purified by silica gel plug column (2.5 cm ID X 6 cm) using a solvent gradient of 19:1(50 mL) to 9:1 (100 mL) to 4:1 (100 mL) to 3:1 (100 mL) to 7:3 (100 mL) hexanes/EtOAc to afford the product, compound **IV-B** (97 mg, 0.312 mmol, 63.3% yield).

[0224] Method C: A mixture of compound **III-1B** (500 mg, 1.40 mmol) and $LiBF_4$ (200 mg, 2.1 mmol) in CH_3CN (6 mL, wet with 2% H_2O) was stirred at 70 °C for 1.5 to 2 hrs (the reaction progress can be monitored by LC-MS). The above reaction mixture was then quickly cooled to 0 °C, filtered through a short silica plug and concentrated under reduced pressure. The product was purified by silica gel column chromatography (1.25 cm ID X 5 cm) using a solvent gradient of 19:1 (50 mL) to 9:1 (50 mL) to 4:1 (50 mL) hexanes/EtOAc to afford the purified product, compound **IV-B** (260 mg, 0.84 mmol, 60% yield).

EXAMPLE 7
SYNTHESIS OF COMPOUND (VI-B) ($R^1 = t$ -BUTYL AND $R^2 =$ METHYL)

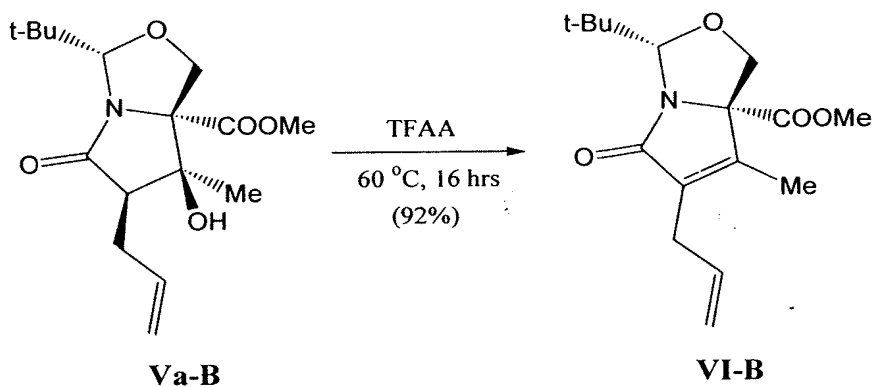


[0225] To a solution of compound **IV-B** (26 g, 83.6 mmol) in dry THF (2.7 L) at RT was added t -BuOK (4.68 g, 41.8 mmol). The reaction mixture was stirred at RT

for 15 min under an atmosphere of N₂ and then quenched with H₂O (900 mL) and extracted with EtOAc (3 X 400 mL). The combined organic phase was washed with saturated brine solution, dried over Na₂SO₄ and concentrated under reduced pressure. The reaction mixture was dissolved in 1:1 ether : hexanes (75 mL each) and transferred to a crystallization dish, where it was allowed to stand and crystallize. After an hour, the crystals (1st crop) were separated by decanting the mother liquor. The crystals were washed with ether (2 X 10 mL) and hexanes (2 X 10 mL). The combined mother liquor and washes was concentrated under reduced pressure and redissolved in 1:1 ether:hexanes (50 mL each) and the crystallization process was repeated the crystallization process as described above. The crystals (2nd crop) were separated by decanting the mother liquor. The mother liquor was chromatographed on a silica gel flash column (30 X 4 cm) using solvent gradient of 19:1 (500 mL) to 9:1 (1 L) to 17:3 (500 mL) EtOAc/hexanes to yield the compound **VI-B**.

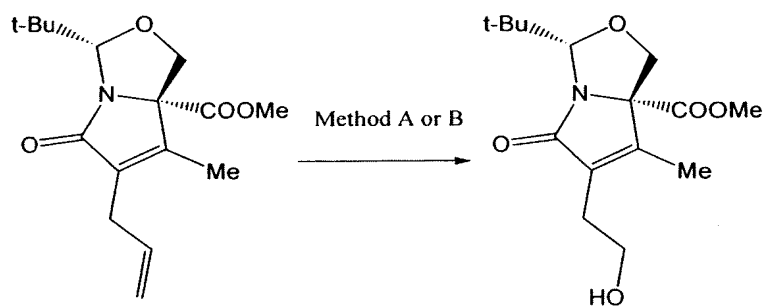
[0226] Compound of **VI-B**: ¹H-NMR (CDCl₃, 500 MHz) (δ): 5.81 (m, 1H), 5.04 (br dd, *J* = 1.5, 7.5 Hz, 1H), 5.02 (s, 1H), 4.78 (d, *J* = 8.5 Hz, 1H), 4.66 (s, 1H), 3.74 (s, 3H), 3.18 (d, *J* = 8.5 Hz, 1H), 2.97 (t, *J* = 6.5 Hz, 1H), 1.83 (s, 3H), 0.91 (s, 9H). See Figure 13. ¹³C-NMR (CDCl₃, 125 MHz) (δ): 178.4, 170.0, 151.9, 133.4, 132.8, 116.1, 96.9, 78.0, 70.5, 52.9, 35.2, 27.6, 24.7, 12.1. See Figure 14. MS (ESI) *m/z* 294 [M+H]⁺.

EXAMPLE 8
SYNTHESIS OF COMPOUND (VI-B) (R¹ = t-BUTYL AND R² = METHYL)



[0227] A solution of compound **V-B** (8 mg, 0.026 mmol) in trifluoroacetic anhydride (TFAA, 0.10 mL) was refluxed at 60 °C for 16 hrs. The reaction mixture was then cooled to 25 °C and concentrated under reduced pressure. The crude residue was purified by silica flash chromatography (EtOAc in hexanes, 10% to 20%) to afford compound **VI-B** (7 mg, 0.024 mmol, 92.3% yield). MS (ESI) m/z 294 $[M+H]^+$.

EXAMPLE 9
SYNTHESIS OF COMPOUND (VII-B) (R^1 = t-BUTYL AND R^2 = METHYL)



Method A: i) OsO₄, NMO, NIO₄; ii) NaBH₄; Method B: i) Ozonolysis; ii) NaBH₄

VI-B

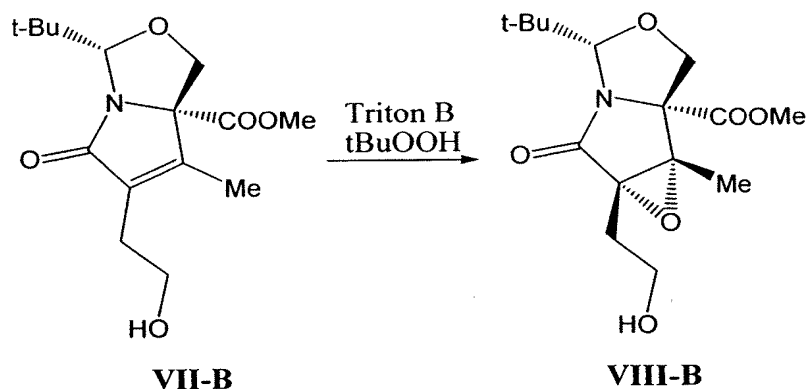
VII-B

[0228] **Method A:** To a solution of compound **VI-B** (40 mg, 0.14 mmol) in THF/H₂O (1:1, 1.0 mL) were added NMO (50% w/w aqueous solution, 0.10 mL, 0.42 mmol) and OsO₄ (2.5% wt.% in 2-methyl-2-propanol, 108 µL, 7 µmol). The resulting mixture was stirred at 5 °C for 15 hours. Then NaIO₄ (150 mg, 0.70 mmol) was added together with phosphate buffer (pH 7.0, 5 mL), the reaction mixture was stirred for an additional 2 hours at room temperature before diluting with ethyl acetate (5 mL) and washing with water (2x2 mL), saturated aqueous Na₂SO₃ (2 mL), and brine (2 mL). The organic layer was dried over MgSO₄, concentrated under reduced pressure and dried by high vacuum. The crude residue was re-dissolved in THF /H₂O ((2:1; 3 mL), then NaBH₄ (16 mg, 0.42 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (2 X 2 mL) followed by CH₂Cl₂ (3 X 2 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure to obtained a crude residue which was purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford compound **VII-B** (33 mg,

0.11 mmol, 78% overall yield). Compound **VII-B** was characterized by ^1H and ^{13}C NMR. See Figures 15 and 16. MS (ESI) m/z 298 $[\text{M}+\text{H}]^+$.

[0229] Method B: A solution of compound **VI-B** (1.0 g, 3.40 mmol) in THF (20 mL) was treated with ozone at $-80\text{ }^\circ\text{C}$ for 0.5 hrs (the O_3 was generated by OL80F ozonation equipment and the ozonolysis reaction progress was monitored by TLC). To this reaction mixture was added NaBH_4 (0.64 g, 17.0 mmol) followed by MeOH (5 mL) at $-80\text{ }^\circ\text{C}$, then the reaction mixture was slowly warmed up to $25\text{ }^\circ\text{C}$ and stirred for 30 mins at this temperature. The above reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 X 20 mL) followed by CH_2Cl_2 (3 X 20 mL). The organic phase was dried over MgSO_4 and concentrated under reduced pressure. The crude residue was purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford **VII-B** (750 mg, 2.53 mmol, 74% yield) with recovery of some starting material **VI-B** (150 mg, 0.51 mmol). MS (ESI) m/z 298 $[\text{M}+\text{H}]^+$.

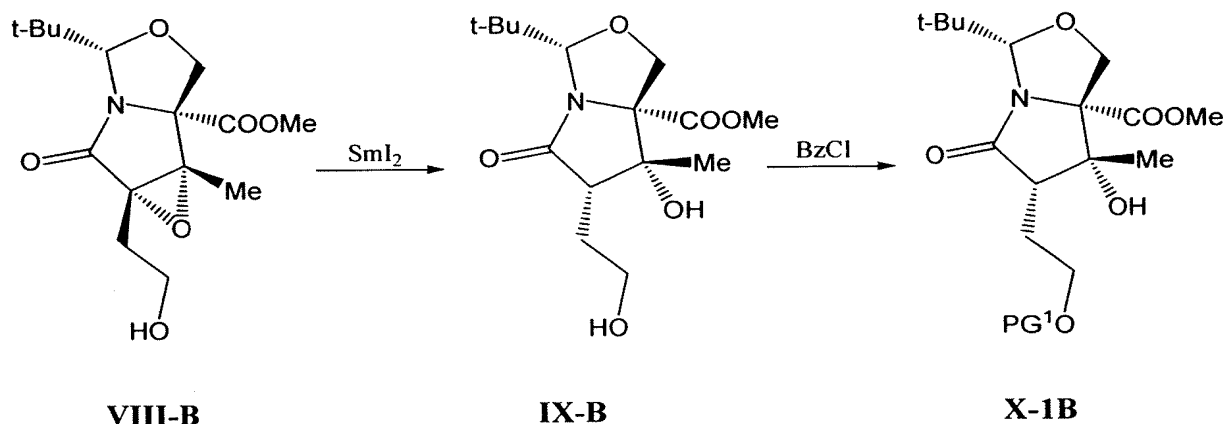
EXAMPLE 10
SYNTHESIS OF COMPOUND (VIII-B) ($\text{R}^1 = t\text{-BUTYL}$ AND $\text{R}^2 = \text{METHYL}$)



[0230] To a concentrated suspension of Triton B (benzyltrimethyl ammonium hydroxide, 80 wt% in methanol, 1.41 g, 8.42 mmol) were added THF (0.5 mL) and *t*-butyl hydroperoxide solution (5-6 M in decane, 4.21 mL, 21.04 mmol) and the reaction mixture was stirred for 10 minutes at room temperature. A solution of compound **VII-B** (1.25 g, 4.21 mmol) in THF (0.1 mL) was added to the above reaction mixture and stirred at room temperature for 18 hours. The reaction mixture was concentrated directly under reduced pressure to obtain a crude residue, which was purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford compound **VIII-B** (130 mg,

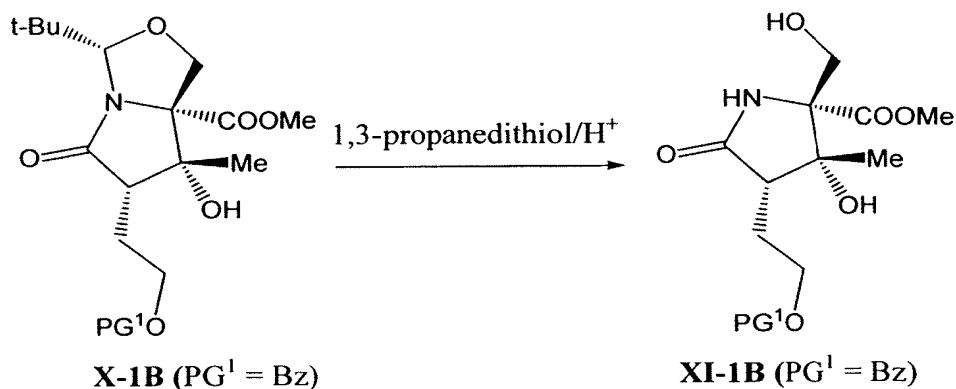
0.42 mmol, 10% Yield) and some starting material **VII-B** (620 mg, 2.08 mmol). The product was characterized by ^1H and ^{13}C NMR. See Figures 17 and 18. The stereochemistry was confirmed by NOESY. See Figure 19. MS (ESI) m/z 314 $[\text{M}+\text{H}]^+$.

EXAMPLE 11
SYNTHESIS OF COMPOUND (X-1B)
 ($\text{PG}^1 = \text{Bz}$, $\text{R}^1 = \text{t-BUTYL}$ AND $\text{R}^2 = \text{METHYL}$)



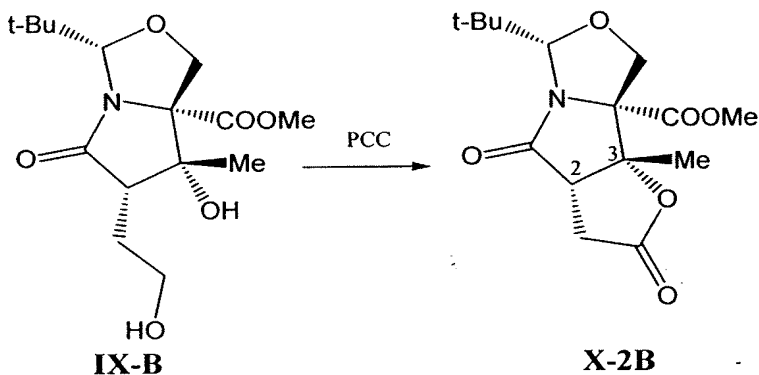
[0231] To a solution of compound **VIII-B** (150 mg, 0.48 mmol) in THF/MeOH (1:1, 2.0 mL) was added Samarium (II) iodide (0.1 M in THF, 14.4 mL, 1.44 mmol) at -80°C and the reaction mixture was stirred at this temperature for 30 minutes. The reaction was then quenched with aqueous NaHCO_3 (10 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with EtOAc (2 X 20 mL). The organic phase was dried over MgSO_4 , concentrated under reduced pressure and dried by high vacuum to yield compound **IX-B** as crude residue. The crude residue was re-dissolved in CH_2Cl_2 (3 mL), pyridine (116 μL , 1.44 mmol) was added, followed by addition of an appropriate protecting group reactant such as benzoyl chloride (BzCl , 100 μL , 0.86 mmol). The resulting reaction mixture was stirred at room temperature for 15 hours. This reaction mixture was then directly concentrated under reduced pressure and the resulting crude product was purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford compound **X-1B** ($\text{PG}^1 = \text{Bz}$) (190 mg, 0.45 mmol, 94% overall yield from **VIII-B**). Compound **X-1B** ($\text{PG}^1 = \text{Bz}$) was characterized by both ^1H and ^{13}C NMR spectra. See Figures 20 and 21. The stereochemistry of compound **X-1B** ($\text{PG}^1 = \text{Bz}$) was also confirmed by NOESY. See Figure 22. MS (ESI) m/z 420 $[\text{M}+\text{H}]^+$.

EXAMPLE 12
SYNTHESIS OF COMPOUND (XI-1B) (PG¹ = Bz, R² = METHYL)



[0232] To a solution of compound **X-1B** (PG¹ = Bz) (15 mg, 36 μmol) in $\text{CF}_3\text{CH}_2\text{OH}$ (0.5 mL) were added 1,3-propanedithiol (500 μL) and a catalytic amount of aqueous HCl (12 N, 2 μL). The reaction mixture was stirred at 60°C for 1 hr, concentrated under reduced pressure and the resulting crude product was then purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford compound **XI-1B** (PG¹ = Bz) (11 mg, 31 μmol , 87%). The product was characterized by ¹H and ¹³C NMR. See Figures 23 and 24. MS (ESI) m/z 352 [M+H]⁺.

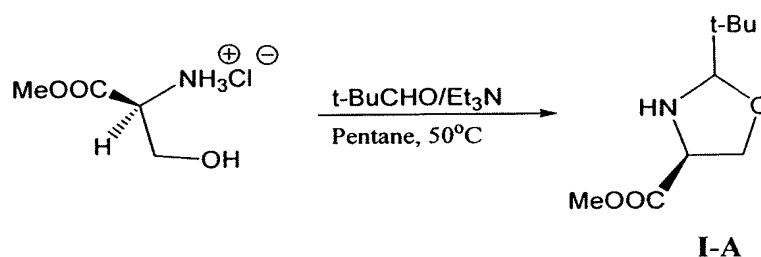
EXAMPLE 13
SYNTHESIS OF COMPOUND (X-2B) (R¹ = t-BUTYL AND R² = METHYL)



[0233] To a solution of compound **IX-B** (32.0 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) with dried 4A molecular sieves (0.10 g) was added pyridinium chlorochromate (PCC, 88 mg, 0.40 mmol). The reaction mixture was stirred at 25°C for 16 hrs,

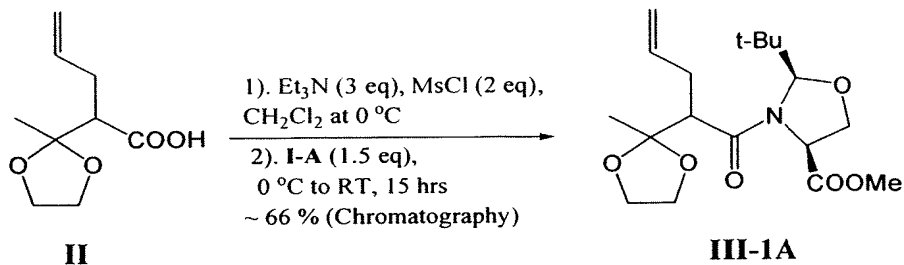
concentrated under reduced pressure and the resulting crude product was then purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford lactone compound **X-2B** (25 mg, 0.08 mmol, 80% yield), which was crystallized in ethyl ether/hexane (3:1, 4.0 mL) at 4 °C. The product was characterized by ^1H and ^{13}C NMR, see Figures 25 and 26, and the stereochemistry was confirmed by X-ray crystallography, see Figure 27; MS (ESI) m/z 312 $[\text{M}+\text{H}]^+$. Thus, the stereochemistry of the C-2 and C-3 carbon centers can be established using the methods and materials in Examples 1-12.

EXAMPLE 14
SYNTHESIS OF (I-A) ($\text{R}^1 = t\text{-BUTYL}$ AND $\text{R}^2 = \text{METHYL}$)



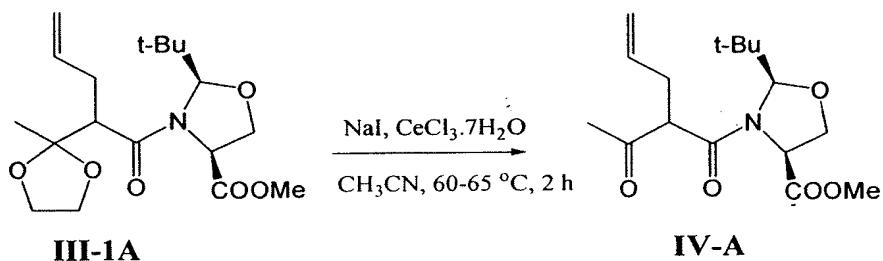
[0234] To a suspension of L-serine methylester hydrochloride (1.88 g, 0.012 mmol) in pentane (30 mL) at room temperature were added *t*-butyl aldehyde (1.57 g, 0.018 mmol) and Et_3N (1.47 g, 0.015 mmol). The reaction mixture was refluxed for 15 hrs at 50 °C using Dean-Stark apparatus. The resulting reaction mixture was cooled to room temperature, filtered through celite, and the celite cake was washed with pentane (2 x 10 mL). The combined filtrate was concentrated under reduced pressure and dried under high vacuum to afford compound **I-A** (1.95 g, 0.01 mmol, 86.9% yield) as clear oil, which can be used without further purification. The compound **I-A** was characterized by ^1H -NMR (CDCl_3 , 500 MHz) and ^{13}C -NMR (CDCl_3 , 125 MHz). See Figures 28 and 29.

EXAMPLE 15
SYNTHESIS OF COMPOUND (III-1A) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



[0235] To a solution of compound **II** (1.0 g, 5.32 mmol) in dry CH_2Cl_2 (15 mL) at $0\text{ } ^\circ\text{C}$ were added Et_3N (2.22 mL, 15.96 mmol) and methanesulfonyl chloride (0.82 mL, 10.6 mmol) and the solution was stirred for about 10 min. Compound **I-A** (1.09 g, 5.85 mmol) was then added; the reaction mixture was allowed to warm to room temperature slowly and stirred for about 15 hrs. Then the reaction mixture was quenched with H_2O (25 mL) and extracted with CH_2Cl_2 (3 X 15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to yield **III-1A** as a mixture of two diastereomers. The crude product was purified by silica flash chromatography (3 cm ID X 30 cm) using a solvent gradient of 9:1 (50 mL) to 4:1 (50 mL) to 3:1 (100 mL) hexane/ EtOAc to afford the product, compound **III-1A** as a diastereomeric mixture (1.14g, 3.19 mmol, 60% yield). The compound **III-1A** was characterized by $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) and $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz). See Figures 30 and 31. MS (ESI) m/z 356 $[\text{M}+\text{H}]^+$.

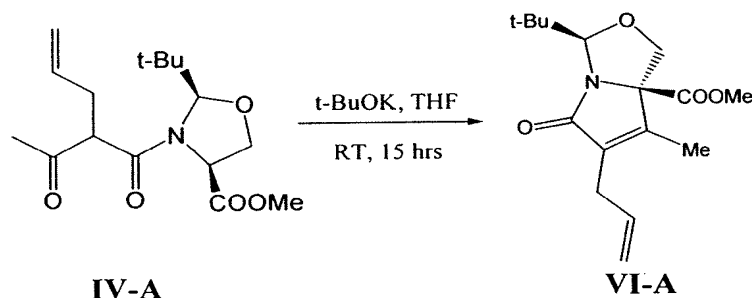
EXAMPLE 16
SYNTHESIS OF COMPOUND (IV-A) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



[0236] To a solution of compound **III-1A** (1.14 g, 3.19 mmol) in CH_3CN (30 mL) were added sodium iodide (0.62 g, 4.15 mmol) and cerium (III) chloride

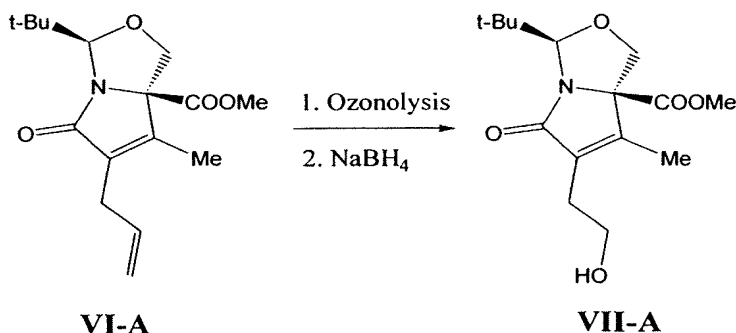
heptahydrate (1.78 g, 4.78 mmol) and the reaction mixture was stirred at 60-65°C for 4 hours (the reaction progress can be monitored by LC-MS). The above reaction mixture was then quenched with water (100 mL) and extracted with EtOAc (3 X 50 mL). The combined organic layer (cloudy) was concentrated under reduced pressure to remove all of the CH₃CN/EtOAc, leaving about 10 mL of H₂O (CH₃CN soluble part), which was further extracted with EtOAc (15 mL). The organic layer was dried over Na₂SO₄, and concentrated under reduced pressure to afford the product, **IV-A** (0.71 g, 2.26 mmol, 71% yield) as a mixture of two diastereomers. If desired, the product can be used for the next step without purification. The compound **IV-A** was characterized by ¹H-NMR (CDCl₃, 500 MHz) and ¹³C-NMR (CDCl₃, 125 MHz) spectra. See Figures 32 and 33. MS (ESI) *m/z* 312 [M+H].

EXAMPLE 17
SYNTHESIS OF COMPOUND (VI-A) (R¹ = t-BUTYL AND R² = METHYL)



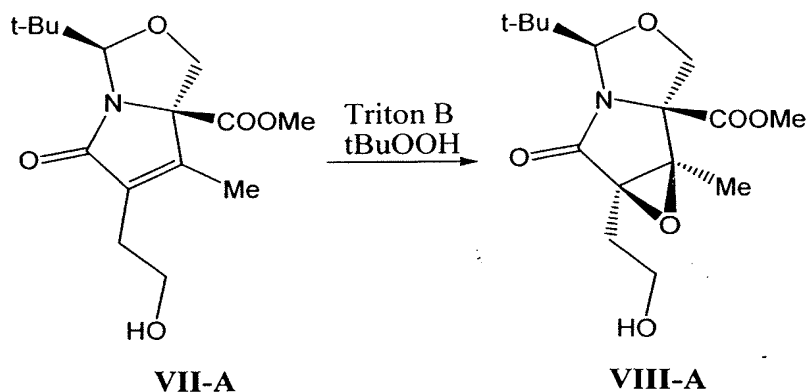
[0237] To a solution of compound **IV-A** (50 mg, 0.16 mmol) in dry THF (5 mL) at RT was added t-BuOK (9.0 mg, 0.08 mmol). The reaction mixture was stirred at RT for 15 hrs under an atmosphere of N₂ and then quenched with H₂O (10 mL) and extracted with EtOAc (3 x 5.0 mL). The combined organic phase was washed with saturated brine solution, dried over Na₂SO₄ and concentrated under reduced pressure). The crude product was purified by silica flash chromatography (5 mm ID x 5 cm) using a solvent gradient of 9:1 (15 mL) to 4:1 (15 mL) hexane/EtOAc to afford the dehydration product **VI-A** (20.0 mg, 0.067 mmol, 42% yield) as the major compound. The compound **VI-A** was characterized by ¹H-NMR (CDCl₃, 500 MHz) and ¹³C-NMR (CDCl₃, 125 MHz) spectra. See Figures 34 and 35. MS (ESI) *m/z* 294 [M+H]⁺.

EXAMPLE 18
SYNTHESIS OF COMPOUND (VII-A) ($R^1 = t$ -BUTYL AND $R^2 =$ METHYL)



[0238] A solution of compound **VI-A** (1.20 g, 4.10 mmol) in THF (30 mL) was treated with ozone at -80°C for 0.5 hours. Then NaBH_4 (0.77 g, 20.5 mmol) and MeOH (6 mL) were added at -80°C , then slowly warmed up to 25°C and stirred for 30 min at this temperature. The above reaction mixture was diluted with H_2O (40 mL) and extracted with EtOAc (2 X 30 mL) followed by CH_2Cl_2 (3 X 30 mL). The organic phase was dried over MgSO_4 and concentrated under reduced pressure, the crude residue was purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford compound **VII-A** (1.0 g, 3.36 mmol, 82% overall yield). Compound **VII-A** was characterized by ^1H and ^{13}C NMR. See Figures 36 and 37. MS (ESI) m/z 298 $[\text{M}+\text{H}]^+$.

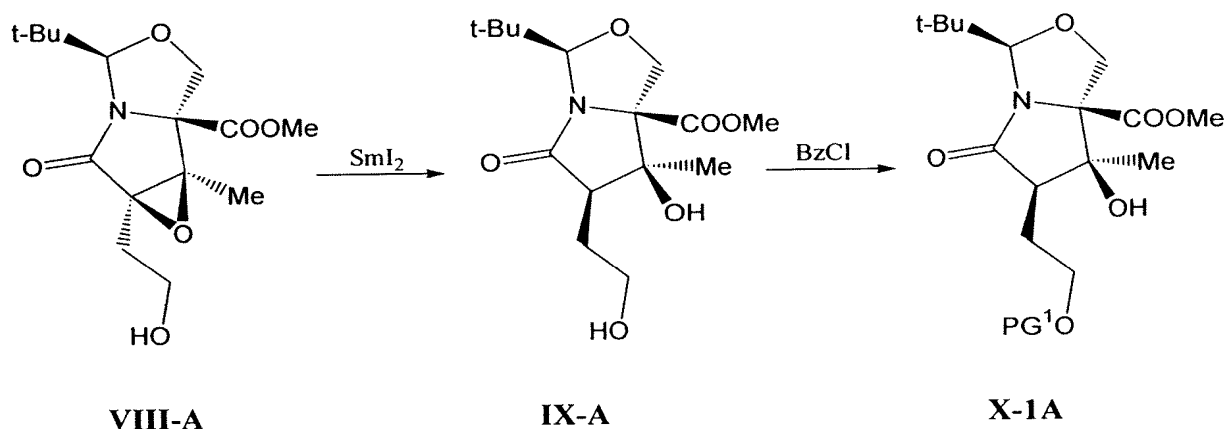
EXAMPLE 19
SYNTHESIS OF COMPOUND (VIII-A) ($R^1 = t$ -BUTYL AND $R^2 =$ METHYL)



[0239] To a concentrated suspension of Triton B (benzyltrimethyl ammonium hydroxide, 80 wt% in methanol, 1.12 g, 6.72 mmol) were added THF (0.6 mL) and t -

butyl hydroperoxide solution (5-6 M in decane, 3.36 mL, 16.8 mmol) and the reaction mixture was stirred for 10 minutes at room temperature. A solution of compound **VII-A** (1.0 g, 3.36 mmol) in THF (0.1 mL) was added to the above reaction mixture and stirred at room temperature for 18 hours. The reaction mixture was concentrated directly under reduced pressure to obtain a crude residue, which was purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford compound **VIII-A** (160 mg, 0.51 mmol; 15.2 % overall yield) and starting material **VII-A** (430 mg, 1.45 mmol). The product was characterized by ^1H and ^{13}C NMR. See Figures 38 and 39. MS (ESI) m/z 314 $[\text{M}+\text{H}]^+$.

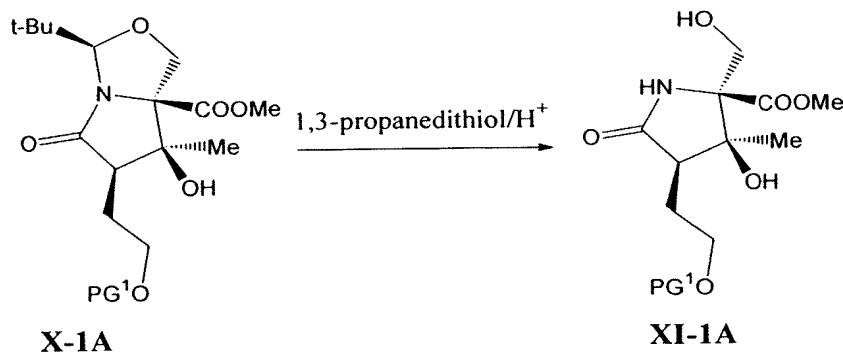
EXAMPLE 20
SYNTHESIS OF COMPOUND (X-1A)
 ($\text{PG}^1 = \text{Bz}$, $\text{R}^1 = \text{t-BUTYL}$ AND $\text{R}^2 = \text{METHYL}$)



[0240] To a solution of compound **VIII-A** (80 mg, 0.26 mmol) in THF/MeOH (1:1, 2.0 mL) was added samarium (II) iodide (0.1 M in THF, 7.6 mL, 0.76 mmol) at -80°C and the reaction mixture was stirred at this temperature for 30 minutes. The reaction was then quenched with aqueous NaHCO_3 (10 mL), $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) at -80°C and extracted with EtOAc (2 X 20 mL) and CH_2Cl_2 (2 x 20 mL). The organic phase was dried over MgSO_4 , concentrated under reduced pressure and dried by high vacuum. The crude residue was re-dissolved in CH_2Cl_2 (2 mL), then pyridine (63 μL , 0.77 mmol) and an appropriate protecting group reactant such as benzoyl chloride (BzCl , 53 μL , 0.46 mmol) were added. The resulting reaction mixture was stirred at room temperature for 15 hours. This reaction mixture was then directly concentrated under reduced pressure

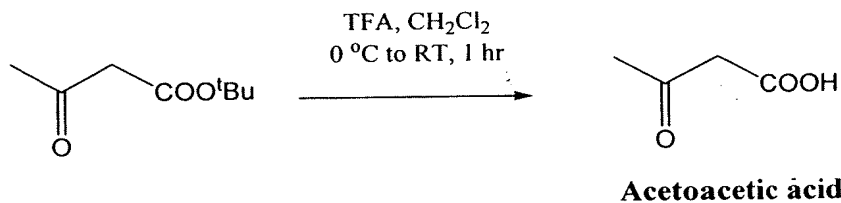
and the resulting crude product was purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford compound **X-1A** ($\text{PG}^1 = \text{Bz}$) (92 mg, 0.22 mmol, 86% overall yield from **VIII-A**). Compound **X-1A** ($\text{PG}^1 = \text{Bz}$) was characterized by both ^1H and ^{13}C NMR spectra. See Figures 40 and 41. MS (ESI) m/z 420 $[\text{M}+\text{H}]^+$.

EXAMPLE 21
SYNTHESIS OF COMPOUND (XI-1A) ($\text{PG}^1 = \text{Bz}$ AND $\text{R}^2 = \text{METHYL}$)



[0241] To a solution of compound **X-1A** ($\text{PG}^1 = \text{Bz}$) (60 mg, 0.14 mmol) in $\text{CF}_3\text{CH}_2\text{OH}$ (0.2 mL) were added 1,3-propanedithiol (0.2 mL) and a catalytic amount of aqueous HCl (12 N, 2 μL). The reaction mixture was stirred at 60°C for 1 hr, concentrated under reduced pressure and the resulting crude product was then purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford compound **XI-1A** ($\text{PG}^1 = \text{Bz}$) (37 mg, 0.10 mmol, 71.4%). The product was characterized by ^1H and ^{13}C NMR. See Figures 42 and 43. MS (ESI) m/z 352 $[\text{M}+\text{H}]^+$.

EXAMPLE 22
SYNTHESIS OF ACETOACETIC ACID

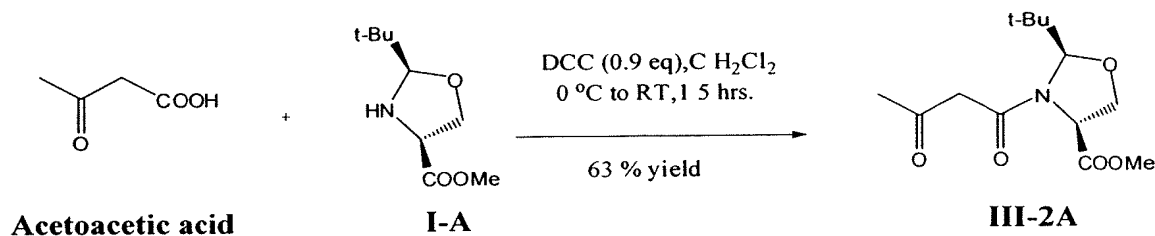


[0242] To a solution of tert-butylacetoacetate (1.60 g, 10.1 mmol) in CH_2Cl_2 (3.0 mL) at 0°C was added trifluoroacetic acid (TFA neat, 3.0 mL, 40.4 mmol), and the solution was stirred for about 5 min. The reaction mixture was then allowed to warm to

room temperature and stirred for one hour. The reaction mixture was directly concentrated under reduced pressure and dried under high-vacuum for about one hour (to remove the residual TFA) to afford the acetoacetic acid (0.9 g, 8.8 mmol, 87% yield) as a light yellow oil. The acetoacetic acid can be used in the next step without purification. The product was characterized by ^1H NMR(CDCl_3 , 500 MHz) δ 11.11 (br s, 1H), 3.51 (s, 2H), 2.29 (s, 3H).

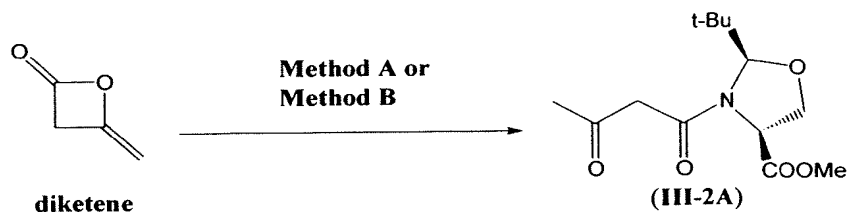
EXAMPLE 23

SYNTHESIS OF COMPOUND (III-2A) ($\text{R}^1 = t\text{-BUTYL}$ AND $\text{R}^2 = \text{METHYL}$)



[0243] To a solution of acetoacetic acid (0.9 g, 8.8 mmol) in dry CH_2Cl_2 (15 mL) at 0°C were added compound I-A (derived from L-serine; 1.65 g, 8.8 mmol) and DCC (1.63 g, 7.92 mmol), and the solution was stirred for about 10 min at this temperature. The reaction mixture was allowed to warm to room temperature slowly and stirred for about 15 hrs. The reaction mixture was then diluted with hexane (150 mL) and filtered via a short celite plug. The filtrate was concentrated under reduced pressure, and the crude product was purified by silica flash chromatography (3 cm ID x 30 cm) using a solvent gradient of 9:1 (50 mL) to 4:1 (150 mL) hexane/EtOAc to afford the compound **III-2A** (1.5 g, 5.53 mmol, 62.8% yield) as a keto-enol tautomers (4:1 ratio). The product was characterized by ^1H NMR. See Figure 51. MS (ESI) m/z 272 $[\text{M}+\text{H}]^+$.

EXAMPLE 24
SYNTHESIS OF COMPOUND (III-2A) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



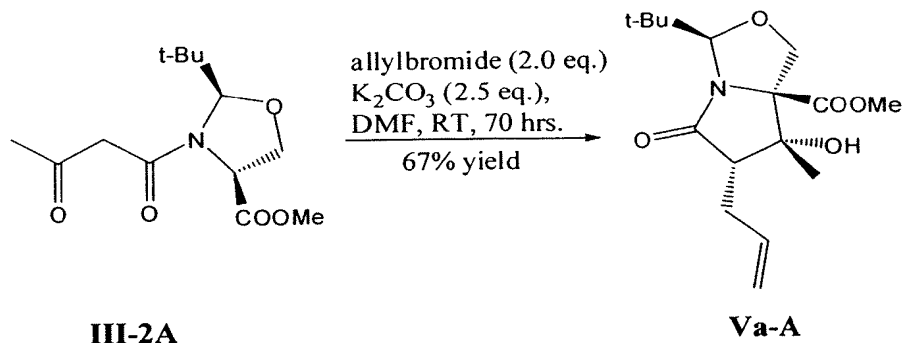
Method A: (I-A) (1.0 eq), Et₃N (0.2 eq), diketene (1.5 eq), THF, 50 °C, 15 hrs;

Method B: (I-A) (1.0 eq), pyridine (0.5 eq), diketene (1.5 eq), benzene, 60 °C, 18 hrs

[0244] Method A: To a solution of I-A (600 mg, 3.19 mmol) in dry THF (3.0 mL) was added diketene (0.37 mL, 4.78 mmol) and Et₃N (89 μ L, 0.64 mmol), the reaction mixture was stirred at 50 °C for 15 hrs. The reaction mixture was cooled to room temperature and diluted with ice cold hydrochloric acid (0.5 N, 15 mL), then extracted with dichloromethane (3 x 15 mL), the combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography (3 cm ID x 30 cm) using a solvent gradient of 9:1 (50 mL) to 4:1 (100 mL) hexane/EtOAc to afford the product **III-2A** (760 mg, 2.80 mmol, 87.7% yield). ¹H-NMR (CDCl₃, 500 MHz).

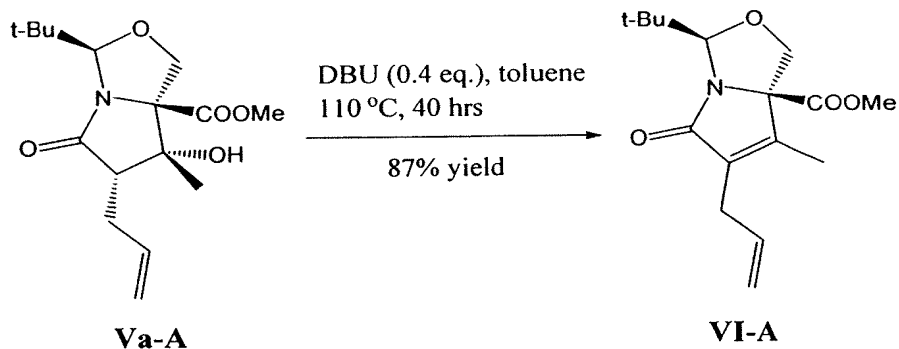
[0245] Method B: To a solution of I-A (4.0 g, 0.021 mol) in dry benzene (20.0 mL) was added diketene (2.46 mL, 0.032 mol) and pyridine (0.86 mL, 0.011 mol), the reaction mixture was stirred at 60 °C for 18 hrs. The reaction mixture was cooled to room temperature and directly concentrated under reduced pressure. The crude product was purified by silica flash chromatography (3 cm ID x 30 cm) using a solvent gradient of 9:1 (150 mL) to 4:1 (200 mL) hexane/EtOAc to afford the product **III-2A** (4.30 g, 0.016 mol, 76.2% yield). The ¹H-NMR is the same as in Figure 51.

EXAMPLE 25
SYNTHESIS OF COMPOUND (Va-A) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



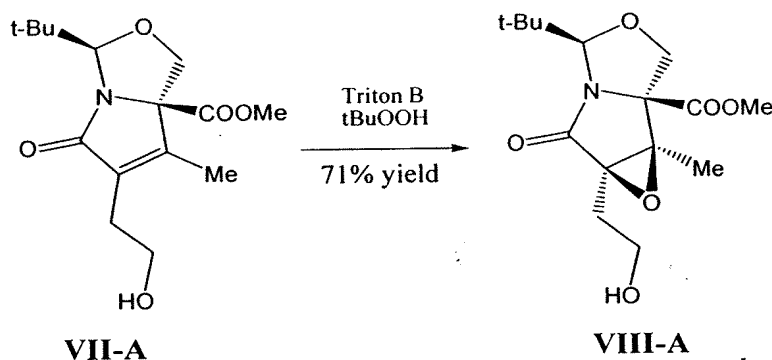
[0246] To a solution of a compound **III-2A** (1.10g, 4.06 mmol) in dry DMF (16.0 mL) at RT was added K_2CO_3 (1.40 g, 10.1 mmol) and allylbromide (0.70 mL, 8.12 mmol). The reaction mixture was stirred at RT for 70 hrs under an atmosphere of N_2 and then filtered via a short celite plug. The filtration was concentrated under reduced pressure to yield a crude product which contained compound **Va-A** as major and diastereomers **Vb-A** and **Vc-A** as minor (5-10%). The crude product was chromatographed on a silica gel flash column (30 x 4 cm) using a solvent gradient of 19:1 (100 mL) to 9:1 (200 mL) to 4:1 (300 mL) hexanes/EtOAc to yield the compound **V-A** (840 mg, 2.70 mmol, 66.5% yield) as a white solid. White crystalline solid was obtained from 1:1 diethyl ether:hexanes having a melting point of 114-116°C. $[\alpha]^{22}_D$ -8.4 (c 0.96, CH_3CN); $^1H\text{-NMR}$ ($CDCl_3$, 500 MHz) δ 5.92 (m, 1H), 5.11 (br dd, $J = 1.5, 17.2$ Hz, 1H), 5.01 (d, $J = 10.1$ Hz, 1H), 4.88 (s, 1H), 4.47 (d, $J = 8.8$ Hz, 1H), 4.23 (d, $J = 8.8$ Hz, 1H), 3.74 (s, 3H), 3.04 (t, $J = 6.6$ Hz, 1H), 2.52 (m, 1H), 2.28 (m, 1H), , 1.27 (s, 3H), 0.83 (s, 9H). $^{13}C\text{-NMR}$ ($CDCl_3$, 125 MHz) δ 177.9, 171.8, 136.7, 116.7, 96.7, 80.4, 79.1, 68.0, 53.2, 52.7, 36.5, 28.0, 25.0 (3x CH_3), 23.0. The product was characterized by 1H and ^{13}C NMR. See Figures 52 and 53. MS (ESI) m/z 312 $[M+H]^+$.

EXAMPLE 26
SYNTHESIS OF COMPOUND (VI-A) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



[0247] To a solution of compound V-A (4.28 g, 13.7 mmol) in dry toluene (50 mL) was added DBU (0.83 g, 5.50 mmol). The reaction mixture was refluxed at 110°C under an atmosphere of N₂ for 40 hrs and the reaction mixture was then cooled to RT, concentrated under reduced pressure and the crude product was chromatographed on a silica gel flash column (30 x 4 cm) using a solvent gradient of 19:1 (100 mL) to 9:1 (200 mL) to 4:1 (400 mL) hexanes/EtOAc to afford the product VI-A (3.50 g, 11.9 mmol, 87% yield). The compound VI-A was characterized by ¹H-NMR (CDCl₃, 500 MHz) and ¹³C-NMR (CDCl₃, 125 MHz) spectra. See Figures 34 and 35. MS (ESI) *m/z* 294 [M+H]⁺.

EXAMPLE 27
SYNTHESIS OF COMPOUND (VIII-A) ($R^1 = t\text{-BUTYL}$ AND $R^2 = \text{METHYL}$)



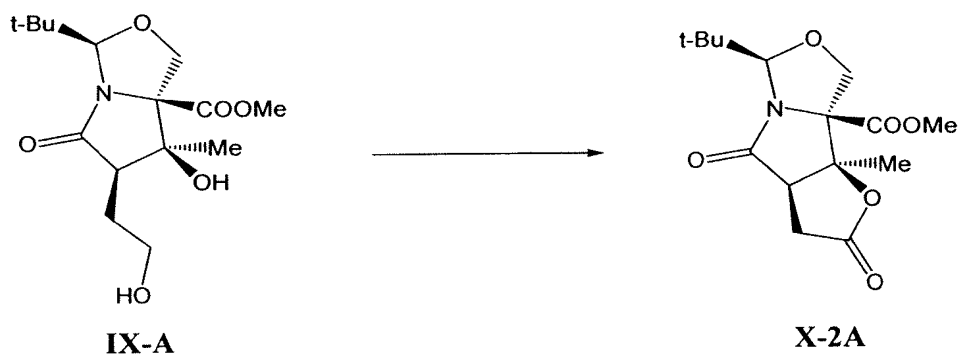
[0248] Triton B (benzyltrimethyl ammonium hydroxide, 80 wt% in methanol, 15 mg, 0.18 mmol) was added to the concentrated *tert*-butyl hydroperoxide solution (ten-fold concentrated* from the original 5-6 M solution in decane, 400 μL, excess) with

extreme safety precautions and then the reaction mixture was stirred for 5 minutes at room temperature. Compound **VII-A** (30 mg, 0.10 mmol) in THF (0.1 mL) was added to the above reaction mixture and stirred at 25 °C for 40 hours. The reaction mixture was concentrated directly under reduced pressure to obtain a crude residue, which was purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford compound **VIII-A** (22 mg, 0.071 mmol, 71% yield). The product was characterized by ¹H and ¹³C NMR. See Figures 38 and 39. MS (ESI) *m/z* 314 [M+H]⁺.

[0249] *Note: *tert*-butyl hydroperoxide was concentrated by a stream of nitrogen at room temperature with extreme personal safety precautions.

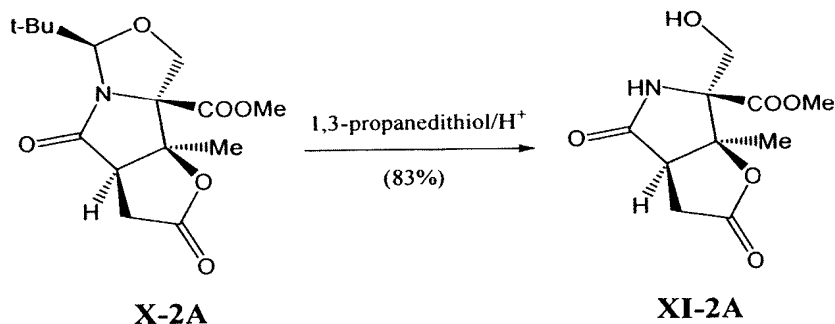
EXAMPLE 28

SYNTHESIS OF COMPOUND (X-2A) (R¹ = *t*-BUTYL AND R² = METHYL)



[0250] To a solution of compound **IX-A** (47 mg, 0.15 mmol) in CH₂Cl₂ (1.0 mL) with dried 4A molecular sieves (0.10 g) was added pyridinium chlorochromate (PCC, 96 mg, 0.45 mmol). The reaction mixture was stirred at 25°C for 16 hrs, concentrated under reduced pressure and the resulting crude product was then purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford **X-2A** (29 mg, 0.125 mmol, 84% yield). The product was characterized by ¹H and ¹³C NMR. See Figures 44 and 45. MS (ESI) *m/z* 312 [M+H]⁺.

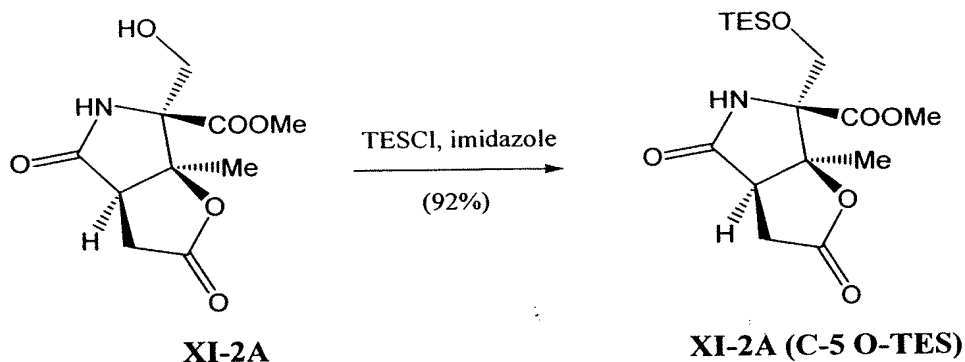
EXAMPLE 29
SYNTHESIS OF COMPOUND (XI-2A) (R^2 = METHYL)



[0251] To a solution of compound **X-2A** (39 mg, 0.12 mmol) in $\text{CF}_3\text{CH}_2\text{OH}$ (1.0 mL) were added 1,3-propanedithiol (1.0 mL) and a catalytic amount of aqueous HCl (12 N, 15 μL). The reaction mixture was stirred at 6 °C for 1.0 hr, concentrated under reduced pressure and the resulting crude product was then purified by silica flash chromatography (EtOAc in hexanes, 20% to 80%) to afford compound **XI-2A** (25 mg, 0.10 mmol, 83% yield). The product was characterized by ^1H and ^{13}C NMR. See Figures 46 and 47. MS (ESI) m/z 244 $[\text{M}+\text{H}]^+$.

EXAMPLE 30
SYNTHESIS OF COMPOUND (XII-2A) (R^2 = METHYL AND C-5 O-TES)

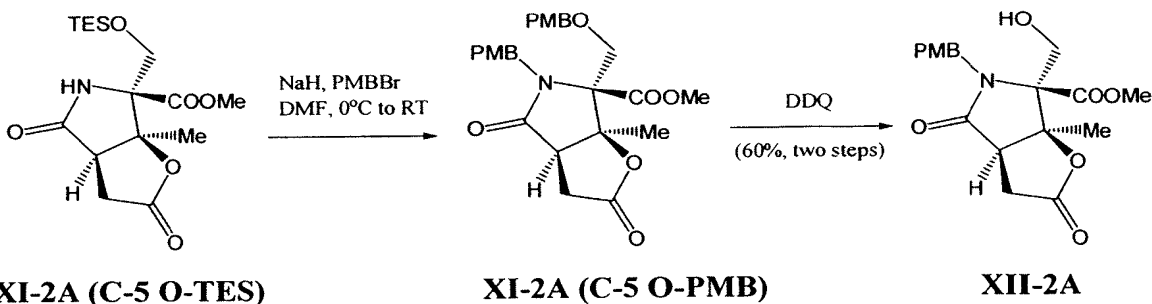
Step 1



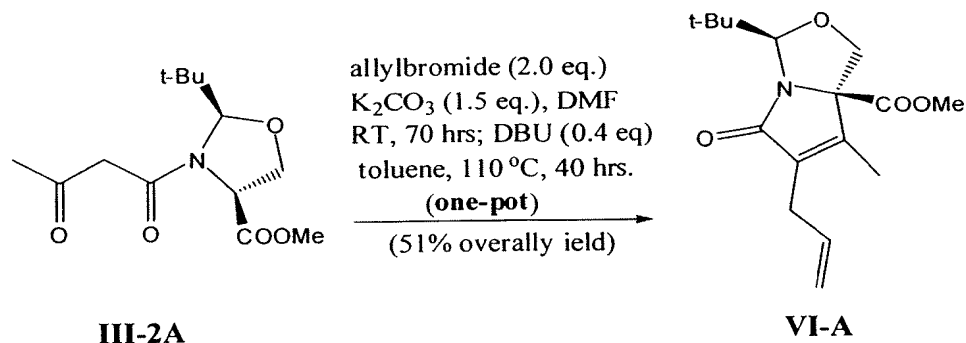
[0252] To a solution of compound **XI-2A** (12 mg, 0.049 mmol) in dry CH_2Cl_2 (2.0 mL) was added imidazole (5 mg, 0.073 mmol) followed by TESCl (9 μL , 0.054 mmol) at 25°C, and the reaction mixture was stirred at 25°C for 15 hours. The reaction mixture was then directly concentrated under reduced pressure and the resulting crude

product was purified by silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford compound **XI-2A (C-5 O-TES)** (16 mg, 0.045 mmol, 92% yield). The product was characterized by ^1H NMR. See Figures 48. MS (ESI) m/z 358 $[\text{M}+\text{H}]^+$.

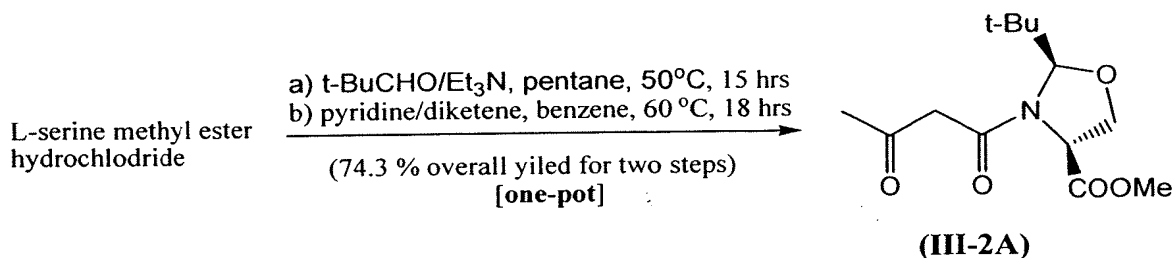
Step 2



[0253] A solution of compound **XI-2A (C-5 O-TES)** (10 mg, 0.028 mmol) in dry DMF (0.1 mL) was added dropwise to a stirred dispersion of NaH (sodium hydride, 60% in mineral oil, 2 mg, 0.042 mmol) in dry DMF (0.2 mL) at 0°C under an argon atmosphere. The reaction mixture was stirred at 0°C for 15 minutes followed by addition of PMBBR (8 μL , 0.056 mmol). The reaction mixture was stirred at 0°C for 1 hour and then allowed to warm up to RT. After reaching RT, the reaction mixture was stirred for 15 hours. Afterwards, the reaction mixture was quenched with glacial acetic acid (0.2 mL) and ice water (0.5 mL) then extracted with CH_2Cl_2 (3 x 1 mL). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure to yield the crude product, compound **XI-2A (C-5 O-PMB)**. The crude compound **XI-2A (C-5 O-PMB)** was directly subjected to the next step without further purification. The compound **XI-2A (C-5 O-PMB)** was redissolved in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (20:1, v/v; 0.2 mL), then DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 13 mg, 0.056 mmol) was added at RT, and the reaction mixture was stirred at this temperature for 6 hours. The reaction mixture was quenched with aqueous NaHCO_3 (1 mL) and extracted with CH_2Cl_2 (3 x 1 mL). The combined organic phase was dried over MgSO_4 and concentrated under reduced pressure, and the resulting crude product was subjected to silica flash chromatography (EtOAc in hexanes, 10% to 50%) to afford compound **XII-2A** (6.2 mg, 0.017 mmol, 60% overall yield for two steps). The product was characterized by ^1H and ^{13}C NMR. See Figures 49 and 50. MS (ESI) m/z 364 $[\text{M}+\text{H}]^+$.

EXAMPLE 31**SYNTHESIS OF COMPOUND (VI-A) ($R^1 = t$ -BUTYL AND $R^2 =$ METHYL)**

[0254] To a solution of **III-2A** (560 mg, 2.06 mmol) in dry DMF (0.50 mL) at RT was added K₂CO₃ (430 mg, 3.10 mmol) and allylbromide (0.36 mL, 4.13 mmol), and the reaction mixture was stirred at RT for 70 hrs under an atmosphere of N₂. The above reaction mixture was directly diluted with dry toluene (25 mL) and was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.12 mL, 0.83 mmol), refluxed at 110 °C for 40 hrs under an atmosphere of N₂ and then cooled to RT. The reaction mixture was filtered via a short celite plug, the filtration was concentrated under reduced pressure, the crude product was chromatographed on a silica gel flash column (30 x 4 cm) using a solvent gradient of 19:1 (100 mL) to 9:1 (200 mL) to 4:1 (200 mL) hexanes/EtOAc to afford the compound **VI-A** (310 mg, 1.06 mmol, 51% overall yield).

EXAMPLE 32**SYNTHESIS OF COMPOUND (III-2A) ($R^1 = t$ -BUTYL AND $R^2 =$ METHYL)**

[0255] To a suspension of (L)-serine methylester hydrochloride (5.50 g, 0.035 mol) in pentane (40 mL) at room temperature were added t-butyl aldehyde (3.62 g, 0.042 mol) and Et₃N (3.93 g, 0.039 mol). The reaction mixture was refluxed for 15 hrs at 50 °C using Dean-Stark apparatus. The resulting reaction mixture was cooled to room

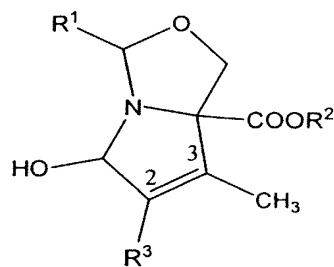
temperature, filtered through celite, and the celite cake was washed with pentane (2 X 20 mL). The combined filtrate was concentrated under reduced pressure and dried under high vacuum to afford crude product as clear oil, which can be used directly for the next step without further purification. To a solution of the above crude product in dry benzene (20.0 mL) was added diketene (4.0 mL, 0.052 mol) and pyridine (1.41 mL, 0.017 mol), the reaction mixture was stirred at 60 °C for 18 hrs. The reaction mixture was cooled to room temperature and directly concentrated under reduced pressure. The crude product was purified by silica flash chromatography (5 cm ID x 400 cm) using a solvent gradient of 9:1 (400 mL) to 4:1 (500 mL) hexane/EtOAc to afford the compound **III-2A** (7.05 g, 0.026 mol, 74.3 % yield). ¹H-NMR (CDCl₃, 500 MHz) was confirmed to be the same as Figure 51.

[0256] It will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present application. Therefore, it should be clearly understood that the forms of the present application are illustrative only and not intended to limit the scope of the present application.

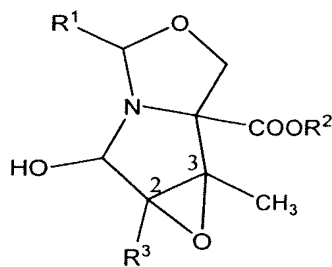
WHAT IS CLAIMED IS:

1. A method of chemical synthesis comprising:

(a) oxidizing a compound of formula (XXII) to form a compound of formula (XXIV):

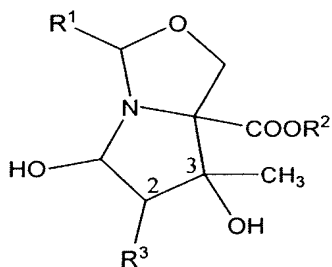


(XXII)



(XXIV); and

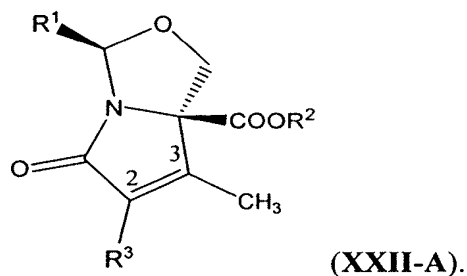
(b) cleaving the epoxide of the compound of formula (XXIV) to form a compound of formula (XV):



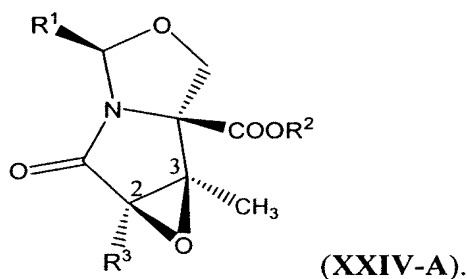
(XXV),

wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; and R^3 is selected from the group consisting of an unsubstituted or substituted C_{1-24} alkyl, an unsubstituted or substituted C_{1-24} alkenyl, an unsubstituted or substituted C_{1-24} alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C_{3-24} cycloalkyl, an unsubstituted or substituted C_{3-24} cycloalkenyl, an unsubstituted or substituted C_{3-24} cycloalkynyl, an unsubstituted or substituted aryl(C_{1-6} alkyl) and an unsubstituted or substituted heteroaryl(C_{1-6} alkyl).

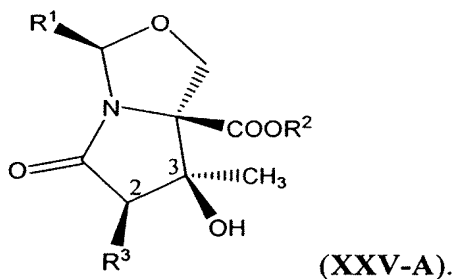
2. The method of Claim 1, wherein the compound of formula (XXII) has the structure and stereochemistry:



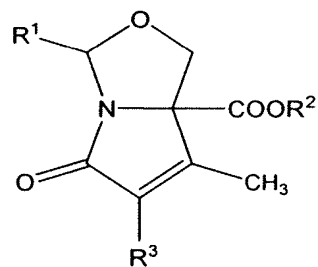
3. The method of any one of Claims 1-2, wherein the compound of formula (XXIV) has the structure and stereochemistry:



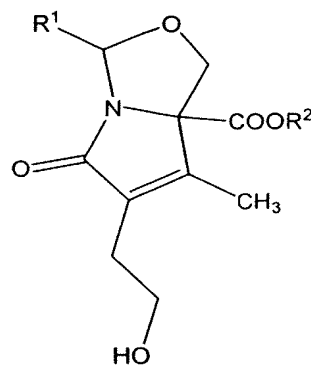
4. The method of any one of Claims 1-3, wherein the compound of formula (XXV) has the structure and stereochemistry:



5. The method of any one of Claims 1-4, further comprising:
oxidizing R^3 of compound of formula (XXII) to an aldehyde and reducing
the aldehyde to an alcohol to form a compound of formula (VII)









(XXII)



(VII)

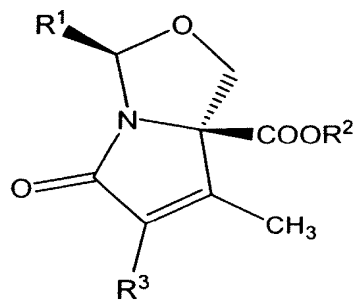
wherein:

R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; R^3

is selected from the group consisting of   R^5 ,   R^5 ,  Ar and  Het , wherein Ar is an unsubstituted or substituted aryl, Het is an unsubstituted or substituted heteroaryl; and R^5 is selected from the group

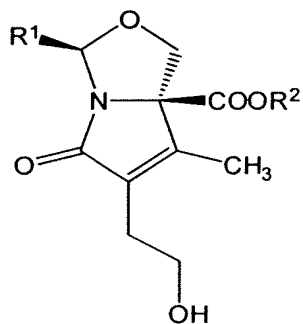
consisting of hydrogen, an unsubstituted or substituted C_{1-24} alkyl, an unsubstituted or substituted C_{1-24} alkenyl, an unsubstituted or substituted C_{1-24} alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C_{3-24} cycloalkyl, an unsubstituted or substituted C_{3-24} cycloalkenyl, an unsubstituted or substituted C_{3-24} cycloalkynyl, an unsubstituted or substituted aryl(C_{1-6} alkyl) and an unsubstituted or substituted heteroaryl(C_{1-6} alkyl).

6. The method of Claim 5, wherein the compound of formula (XXII) has the structure and stereochemistry:



(XXII-A).

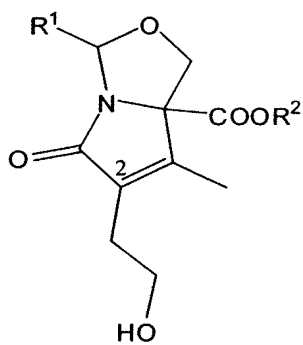
7. The method of any one of Claims 5-6, wherein the compound of formula (VII) has the structure and stereochemistry:



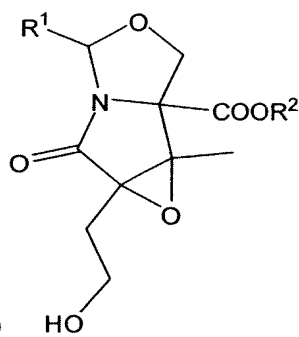
(VII-A).

8. A method of chemical synthesis comprising:

(a) oxidizing a compound of formula (VII) to form a compound of formula (VIII):

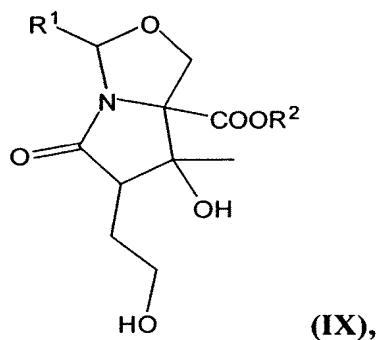


(VII)



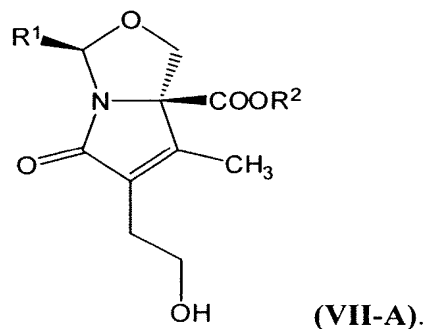
(VIII); and

(b) cleaving the epoxide of the compound of formula (VIII) to form a compound of formula (IX):

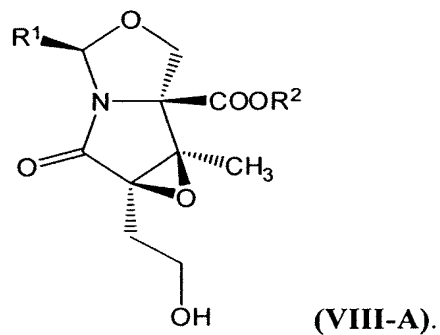


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

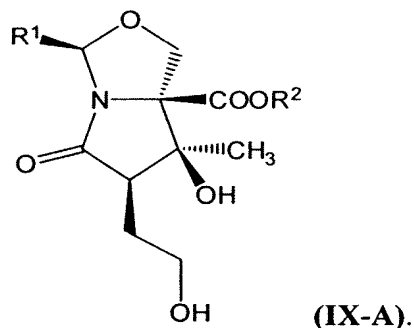
9. The method of Claim 8, wherein the compound of formula (VII) has the structure and stereochemistry:



10. The method of any one of Claims 8-9, wherein the compound of formula (VIII) has the structure and stereochemistry:

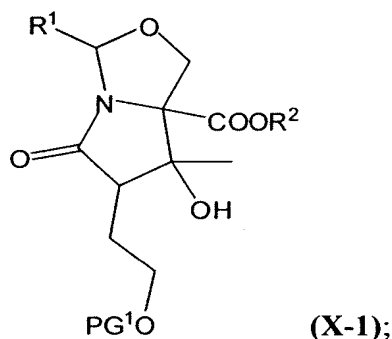


11. The method of any one of Claims 8-10, wherein the compound of formula (IX) has the structure and stereochemistry:

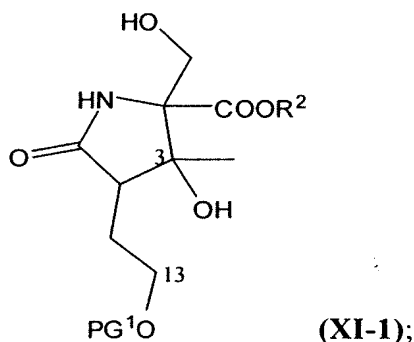


12. The method of any one of Claims 8-11, further comprising:

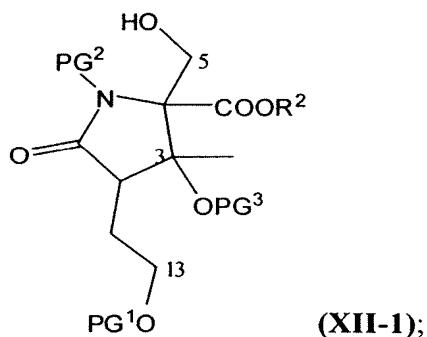
(a) protecting the C-13 primary hydroxy group of the compound of formula (IX) with PG^1 to form a compound of formula (X-1):



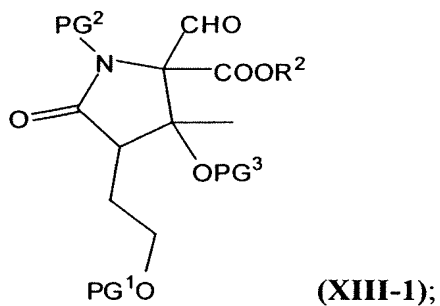
(b) cleaving the acetal group of the compound of formula (X-1) to form a compound of formula (XI-1):



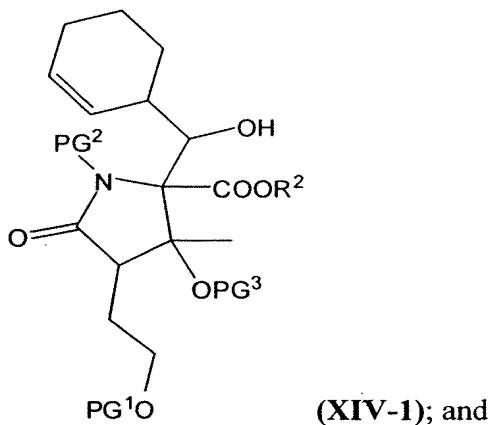
(c) protecting the C-3 tertiary hydroxy group of the compound of formula (XI-1) with PG^3 and protecting the lactam nitrogen of the compound of formula (XI-1) with PG^2 to form a compound of formula (XII-1):



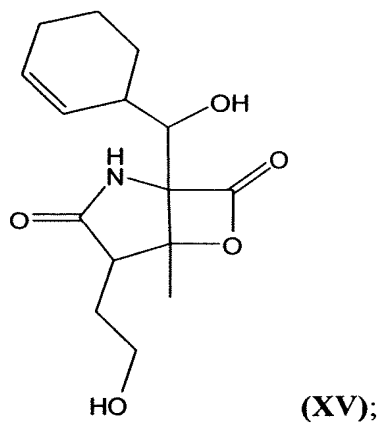
(d) oxidizing the C-5 primary hydroxy group of the compound of formula (XII-1) to form a compound of formula (XIII-1):



(e) reacting the compound of formula (XIII-1) with an organometallic moiety that comprises a cyclohexenyl moiety to form a compound of formula (XIV-1):

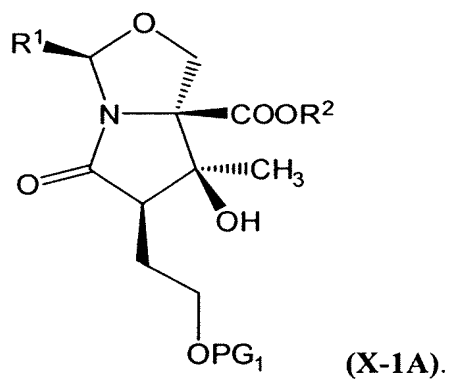


(f) removing the protecting groups, PG^1 , PG^2 and PG^3 , from a compound of formula (XIV-1) and forming a beta-lactone ring to give a compound of formula (XV):

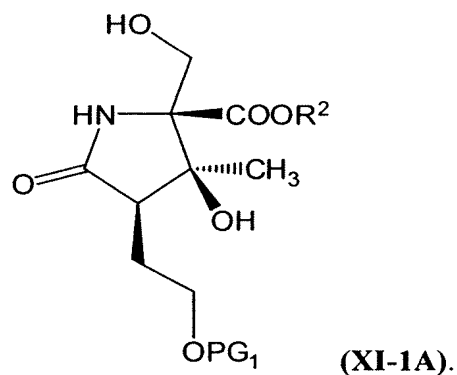


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; and PG^1 , PG^2 and PG^3 are each a separate protecting group.

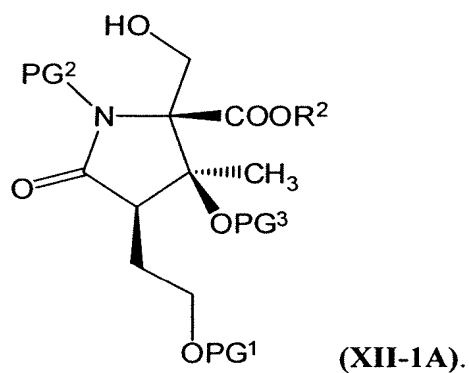
13. The method of Claim 12, wherein the compound of formula (X-1) has the structure and stereochemistry:



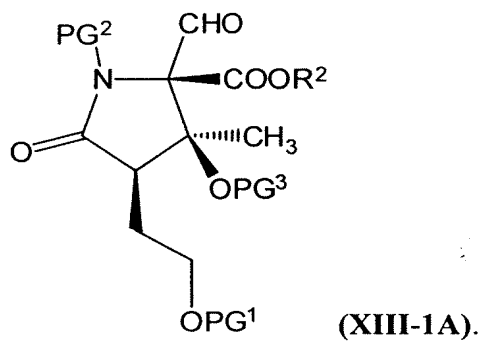
14. The method of any one of Claims 12-13, wherein the compound of formula (XI-1) has the structure and stereochemistry:



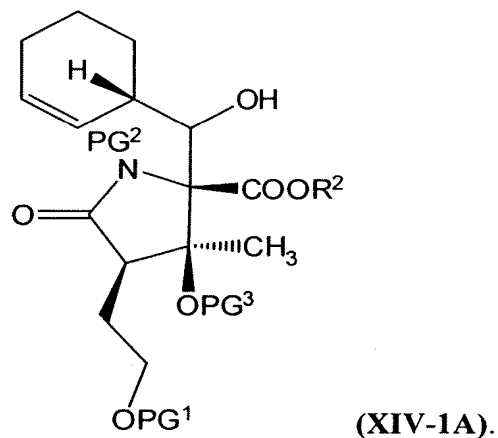
15. The method of any one of Claims 12-14, wherein the compound of formula (XII-1) has the structure and stereochemistry:



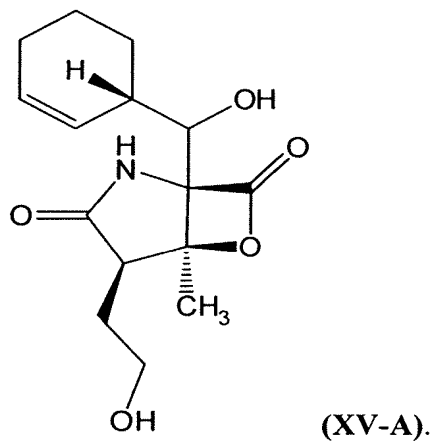
16. The method of any one of Claims 12-15, wherein the compound of formula (XIII-1) has the structure and stereochemistry:



17. The method of any one of Claims 12-16, wherein the compound of formula (XIV-1) has the structure and stereochemistry:

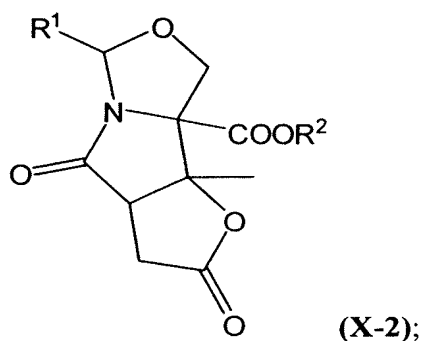


18. The method of any one of Claims 12-17, wherein the compound of formula (XV) has the structure and stereochemistry:

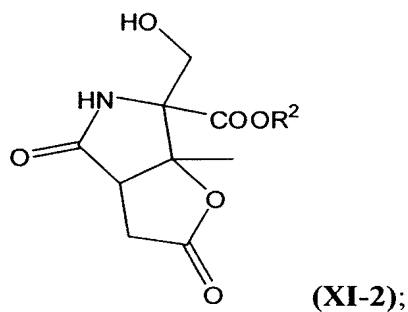


19. The method of any one of Claims 8-11, further comprising:

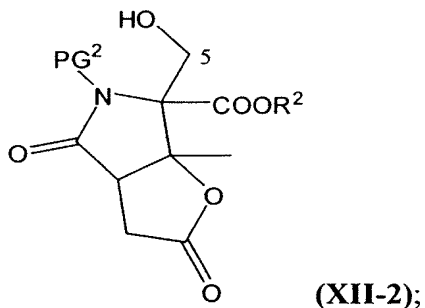
(a) oxidizing the C-13 primary hydroxy group of the compound of formula (IX) and forming a 5-membered lactone via an intramolecular cyclization reaction to give a compound of formula (X-2):



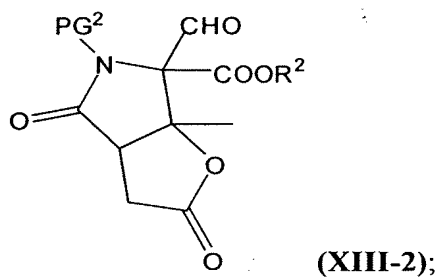
(b) cleaving the aminal group of the compound of formula (X-2) to form a compound of formula (XI-2):



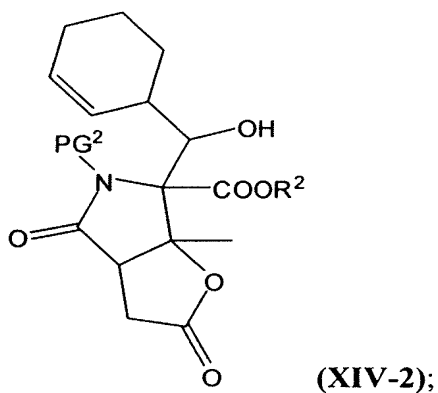
(c) protecting the lactam nitrogen of the compound of formula (XI-2) with PG² to form a compound of formula (XII-2):



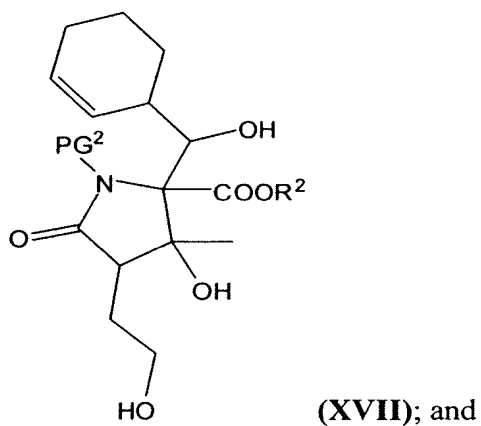
(d) oxidizing the C-5 primary hydroxy group of the compound of formula (XII-2) to form a compound of formula (XIII-2):



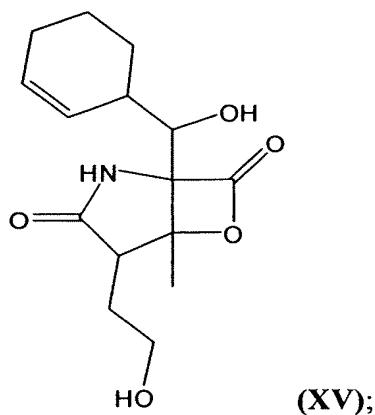
(e) reacting the compound of formula (XIII-2) with an organometallic moiety that comprises a cyclohexenyl moiety to form a compound of formula (XIV-2):



(f) cleaving the 5-membered lactone of the compound of formula (XIV-2) to form a compound of formula (XVII):

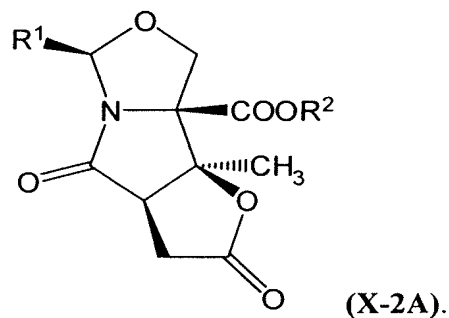


(g) removing PG² from the compound of formula (XVII) and forming a beta-lactone ring to give a compound of formula (XV):

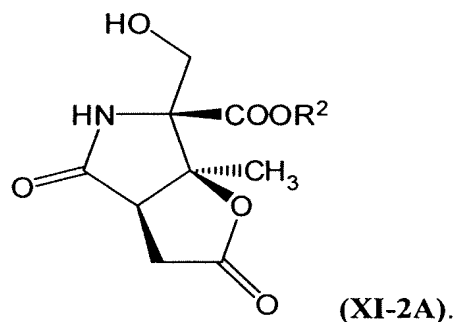


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; and PG^2 is a protecting group.

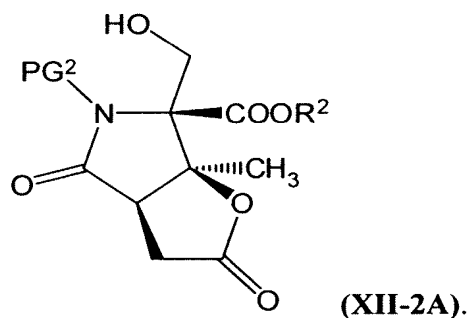
20. The method of Claim 19, wherein the compound of formula (X-2) has the structure and stereochemistry:



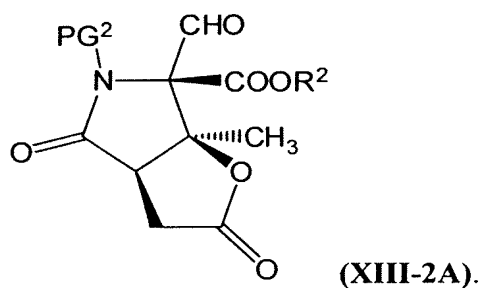
21. The method of any one of Claims 19-20, wherein the compound of formula (XI-2) has the structure and stereochemistry:



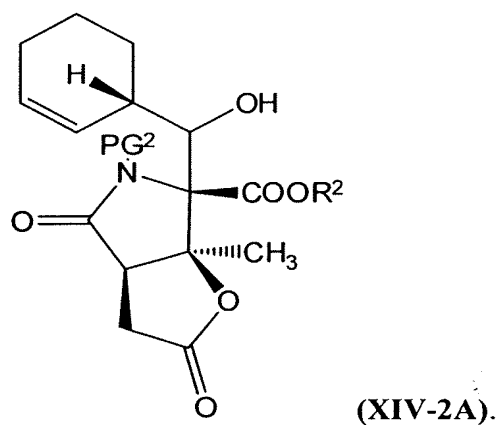
22. The method of any one of Claims 19-21, wherein the compound of formula (XII-2) has the structure and stereochemistry:



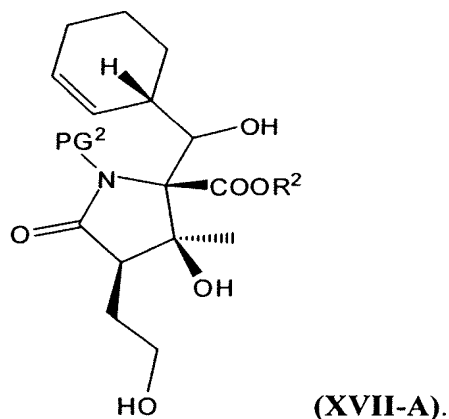
23. The method of any one of Claims 19-22, wherein the compound of formula (XIII-2) has the structure and stereochemistry:



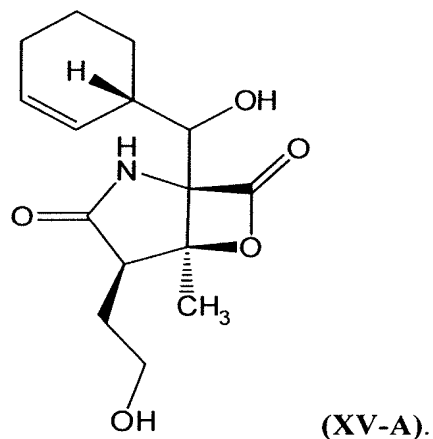
24. The method of any one of Claims 19-23, wherein the compound of formula (XIV) has the structure and stereochemistry:



25. The method of any one of Claims 19-24, wherein the compound of formula (XVII) has the structure and stereochemistry:

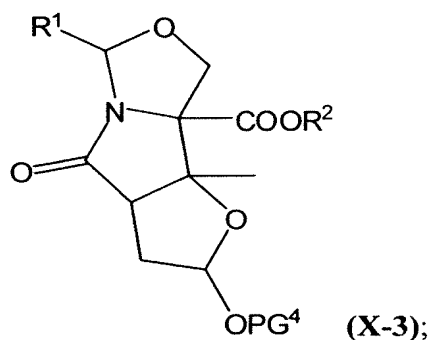


26. The method of any one of Claims 19-25, wherein the compound of formula (XV) has the structure and stereochemistry:

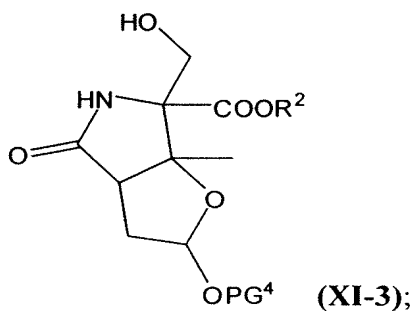


27. The method of any one of Claims 8-11, further comprising:

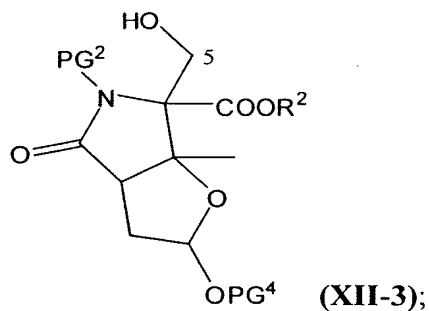
(a) oxidizing the C-13 alcohol to an aldehyde and cyclizing the aldehyde with the C-3 tertiary hydroxy group of the compound of formula (IX) to form a hemi-acetal ring and protecting the secondary hydroxyl group of the hemi-acetal ring to form a compound of formula (X-3):



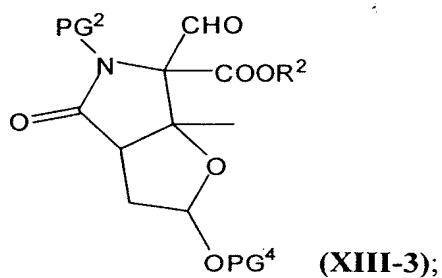
(b) cleaving the aминаl group of the compound of formula (X-3) to form a compound of formula (XI-3):



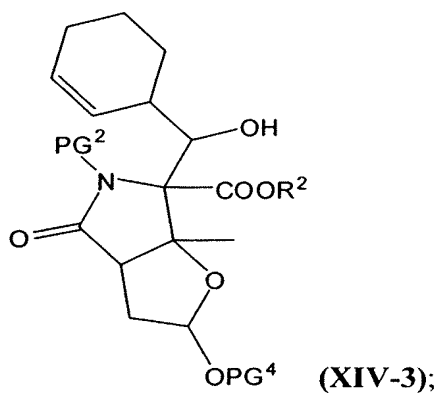
(c) protecting the lactam nitrogen of the compound of formula (XI-3) with PG² to form a compound of formula (XII-3):



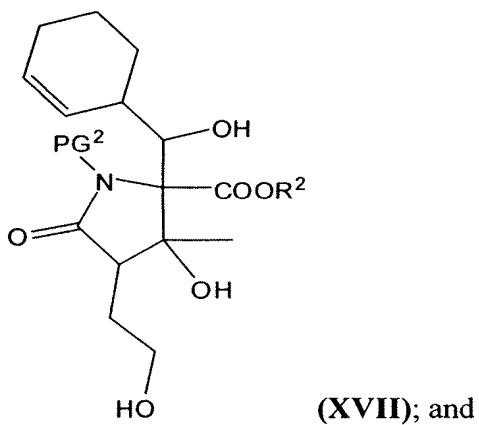
(d) oxidizing the C-5 primary hydroxy group of the compound of formula (XII-3) to form a compound of formula (XIII-3):



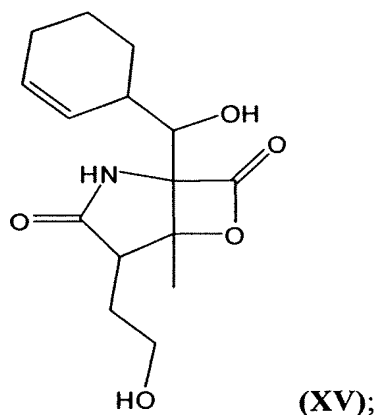
(e) reacting the compound of formula (XIII-3) with an organometallic moiety that comprises a cyclohexenyl moiety to form a compound of formula (XIV-3):



(f) removing the PG⁴ protecting group and reductively cleaving the hemi-acetal ring of the compound of formula (XIV-3) to form a compound of formula (XVII):

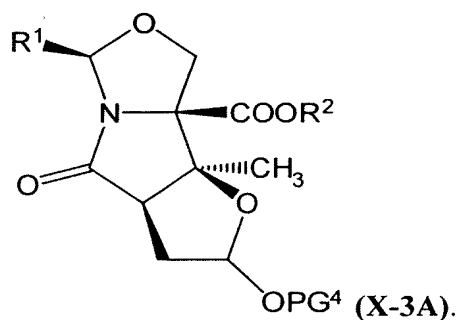


(g) removing PG² from the compound of formula (XVII) and forming a beta-lactone ring to give a compound of formula (XV):

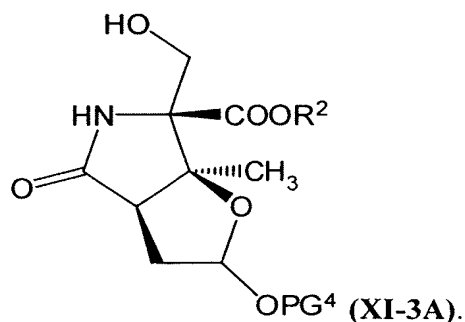


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; and PG^2 and PG^4 are each a separate protecting group.

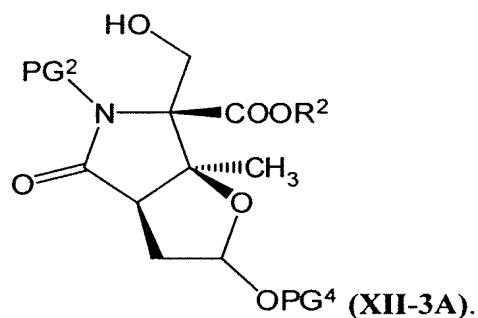
28. The method of Claim 27, wherein the compound of formula (X-3) has the structure and stereochemistry:



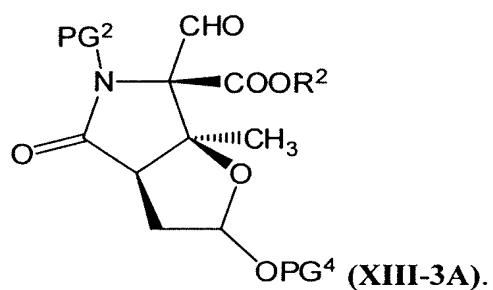
29. The method of any one of Claims 27-28, wherein the compound of formula (XI-3) has the structure and stereochemistry:



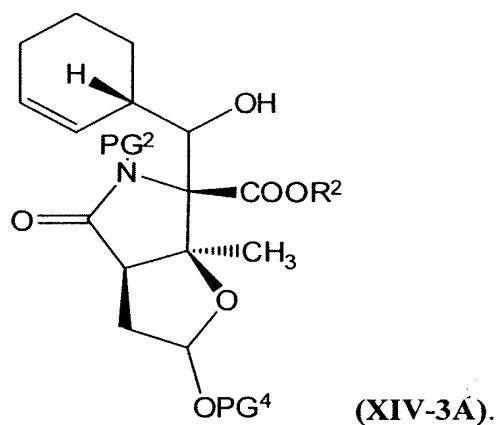
30. The method of any one of Claims 27-29, wherein the compound of formula (XII-3) has the structure and stereochemistry:



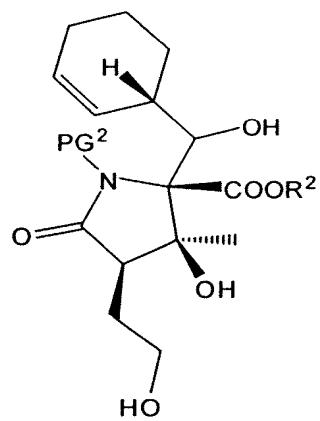
31. The method of any one of Claims 27-30, wherein the compound of formula (XIII-3) has the structure and stereochemistry:



32. The method of any one of Claims 27-31, wherein the compound of formula (XIV-3) has the structure and stereochemistry:

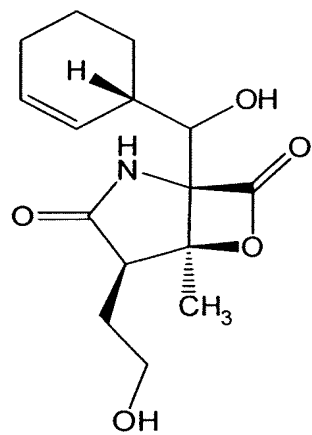


33. The method of any one of Claims 27-32, wherein the compound of formula (XVII) has the structure and stereochemistry:



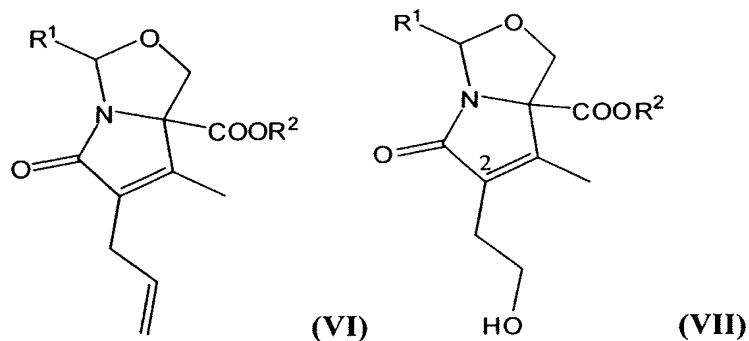
(XVII-A).

34. The method of any one of Claims 27-33, wherein the compound of formula (XV) has the structure and stereochemistry:



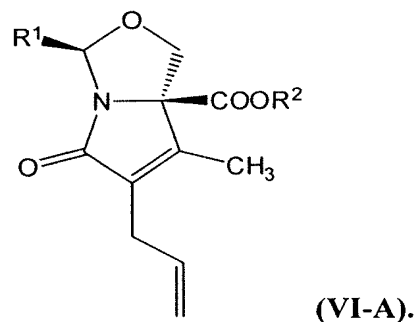
(XV-A).

35. The method of any one of Claims 8-34, further comprising oxidizing the terminal double bond of the allyl substituent at C-2 of a compound of formula (VI) to an aldehyde and reducing the aldehyde to a hydroxy group to form a compound of formula (VII):

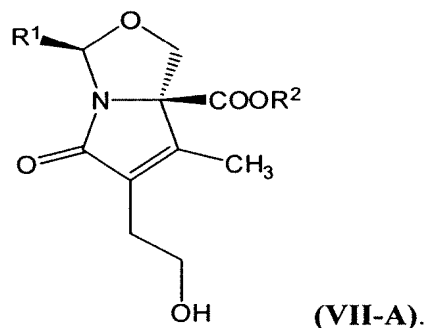


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

36. The method of Claim 35, wherein the compound of formula (VI) has the structure and stereochemistry:

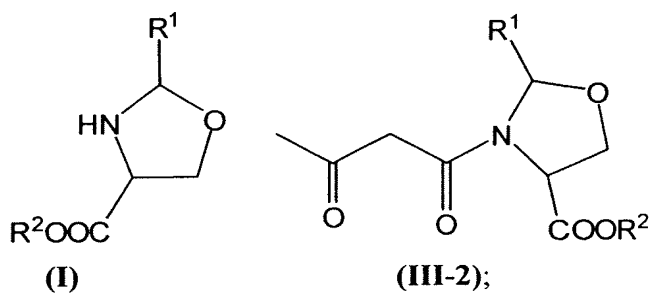


37. The method of any one of Claims 35-36, wherein the compound of formula (VII) has the structure and stereochemistry:

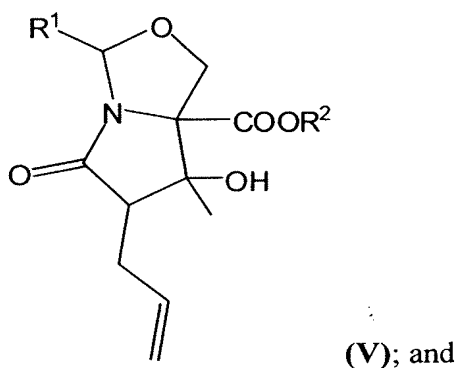


38. The method of any one of Claims 5-37, further comprising:

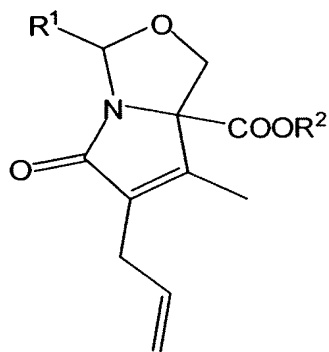
(a) reacting acetoacetic acid with a compound of formula (I) to form a compound of formula (III-2):



(b) alkylating the compound of formula (III-2) with allyl bromide and forming a compound of formula (V) via an intramolecular aldol reaction:

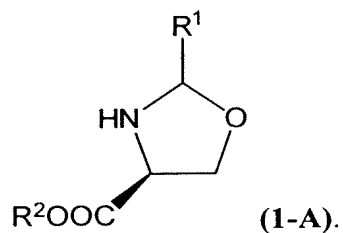


(c) dehydrating the compound of formula (V) to form a double bond between C-2 and C-3 and give a compound of formula (VI):

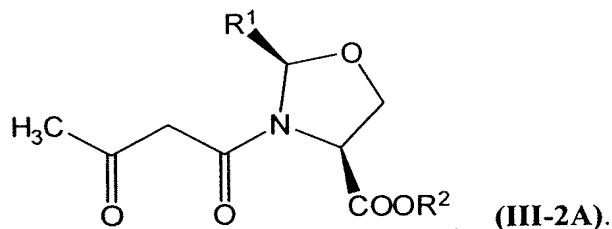


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

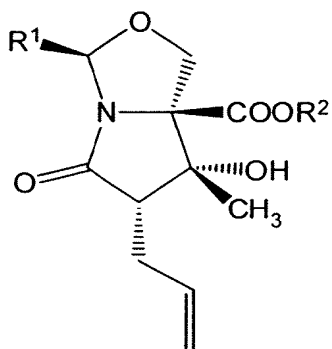
39. The method of Claim 38, wherein the compound of formula (I) has the structure and stereochemistry:



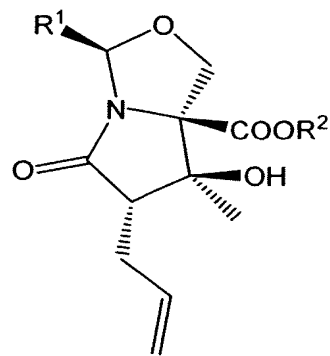
40. The method of any one of Claims 38-39, wherein the compound of formula (III-2) has the structure and stereochemistry:



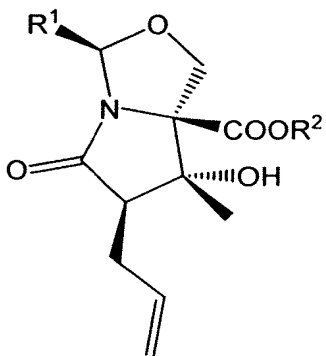
41. The method of any one of Claims 38-40, wherein the compound of formula (V) has a structure and a stereochemistry selected from the group consisting of:



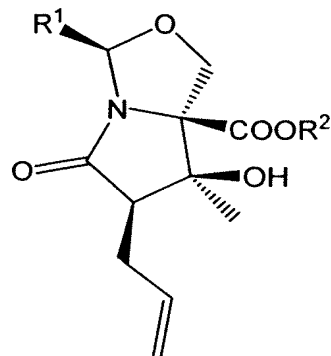
(Va-A),



(Vb-A),

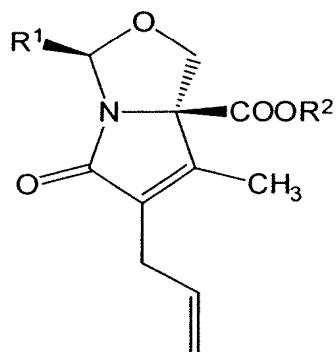


(Vc-A) and



(Vd-A).

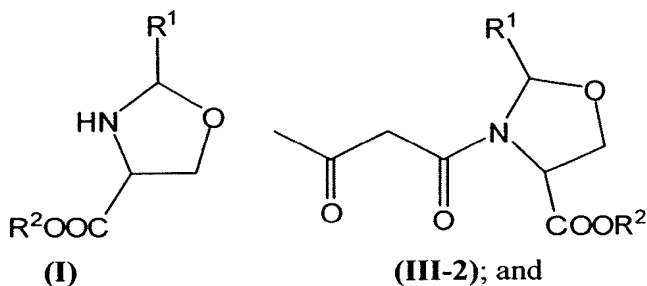
42. The method of any one of Claims 38-41, wherein the compound of formula (VI) has the structure and stereochemistry:



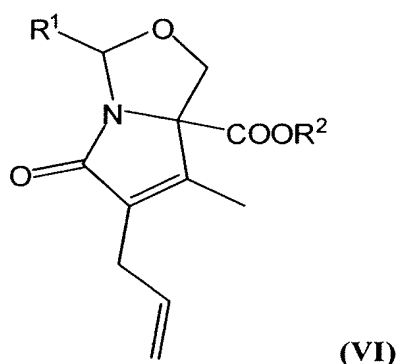
(VI-A).

43. The method of any one of Claims 5-37, further comprising:

(a) reacting acetoacetic acid with a compound of formula (I) to form a compound of formula (III-2); and

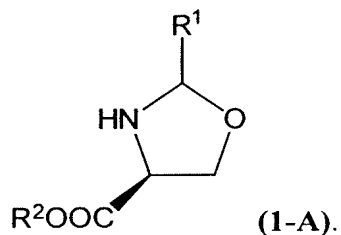


(b) reacting the compound of formula (III-2) with allyl bromide and forming a compound of formula (VI) via an intramolecular aldol condensation reaction:

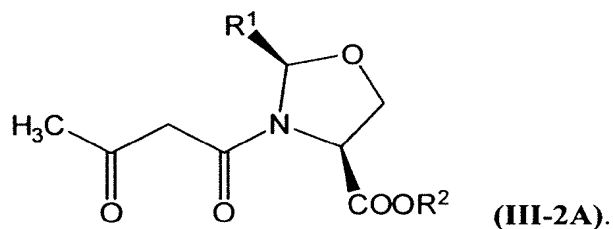


wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

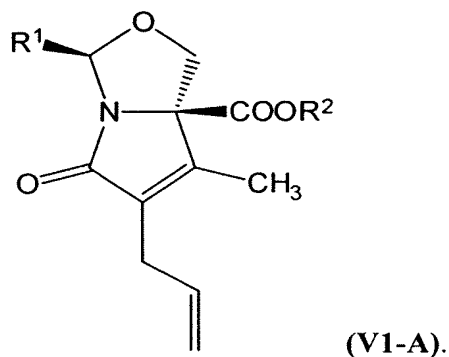
44. The method of Claim 43, wherein the compound of formula (I) has the structure and stereochemistry:



45. The method of any one of Claims 43-44, wherein the compound of formula (III-2) has the structure and stereochemistry:

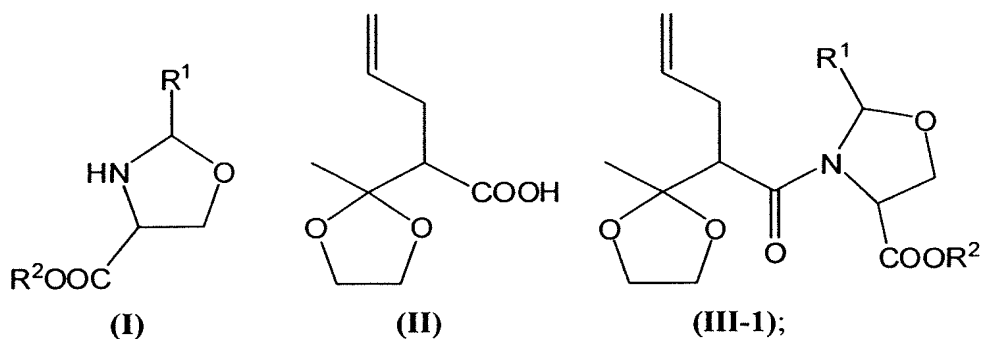


46. The method of any one of Claims 43-45, wherein the compound of formula (VI) has the structure and stereochemistry:

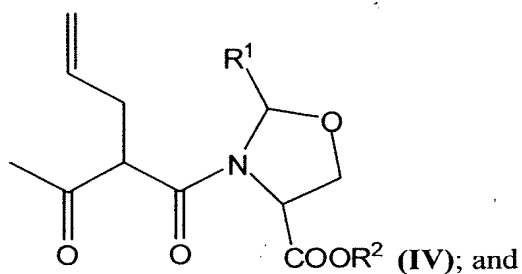


47. The method of any one of Claims 5-37, further comprising:

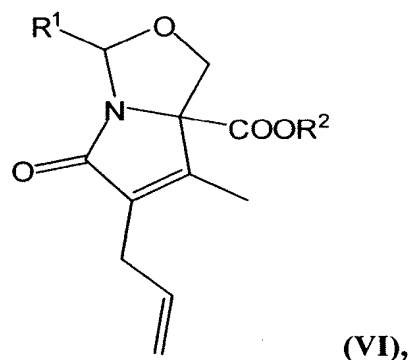
(a) reacting a compound of formula (I) with a compound of formula (II) to form a compound of formula (III-1);



(b) cleaving the 5-membered heterocyclic acetal ring of the compound of formula (III-1) to form a compound of formula (IV):

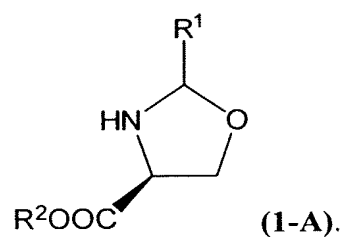


(c) forming a compound of formula (VI) via an intramolecular aldol condensation reaction of the compound of formula (IV):

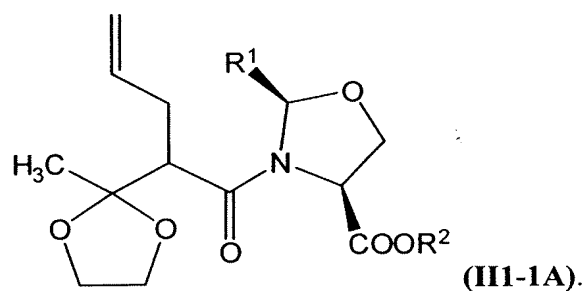


wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; and R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

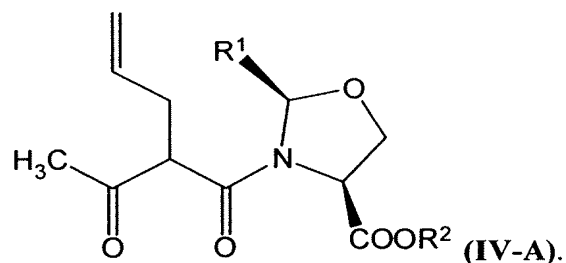
48. The method of Claim 47, wherein the compound of formula (I) has the structure and stereochemistry:



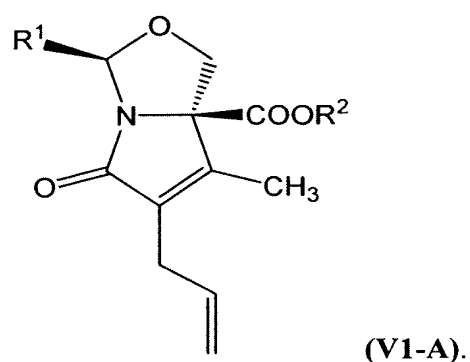
49. The method of any one of Claims 47-48, wherein the compound of formula (III-1) has the structure and stereochemistry:



50. The method of any one of Claims 47-49, wherein the compound of formula (IV) has the structure and stereochemistry:

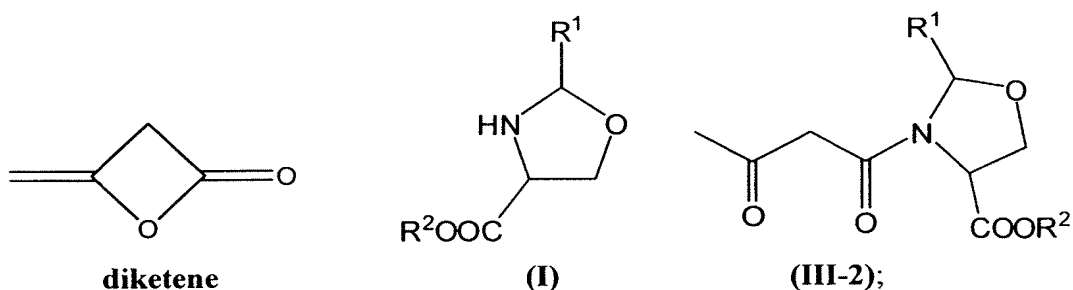


51. The method of any one of Claims 47-50, wherein the compound of formula (VI) has the structure and stereochemistry:

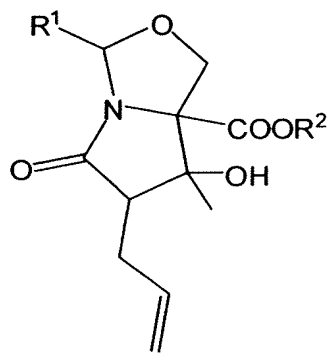


52. The method of any one of Claims 5-37, further comprising:

(a) adding diketene to a compound of formula (I) to form a compound of formula (III-2);

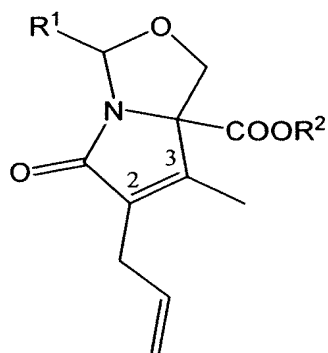


(b) alkylating the compound of formula (III-2) with allyl bromide and forming a compound of formula (V) via an intramolecular aldol reaction; and



(V)

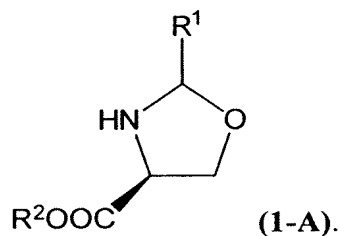
(c) dehydrating the compound of formula (V) to form a double bond between C-2 and C-3 and give a compound of formula (VI):



(VI),

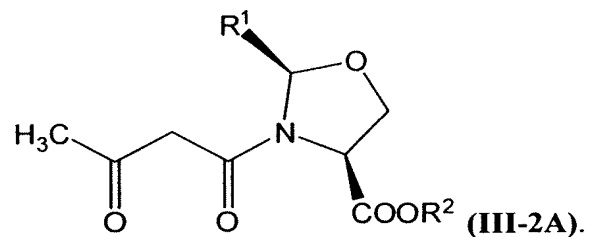
wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; and R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

53. The method of Claim 52, wherein the compound of formula (I) has the structure and stereochemistry:

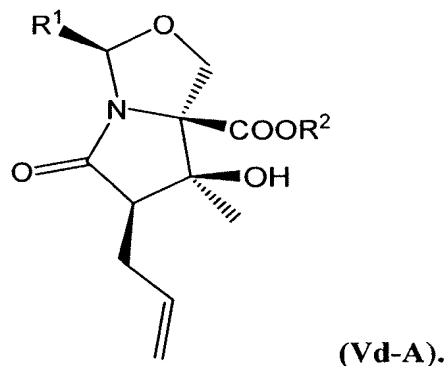
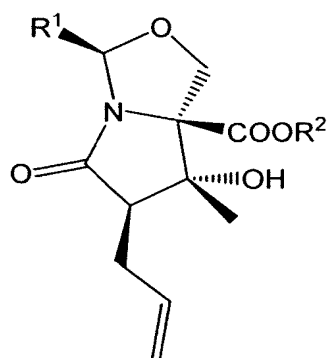
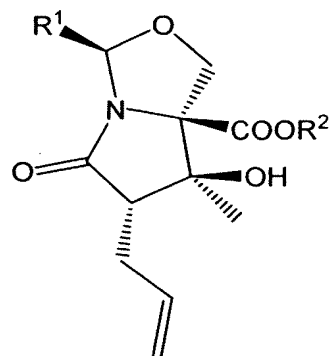
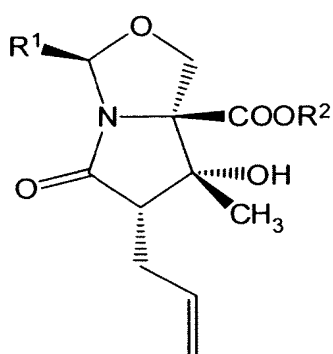


(1-A).

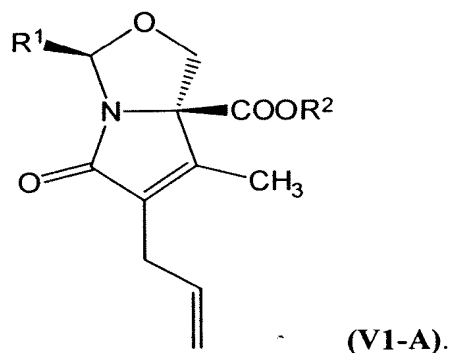
54. The method of any one of Claims 52-53, wherein the compound of formula (III-2) has the structure and stereochemistry:



55. The method of any one of Claims 52-54, wherein the compound of formula (V) has a structure and a stereochemistry selected from the group consisting of:

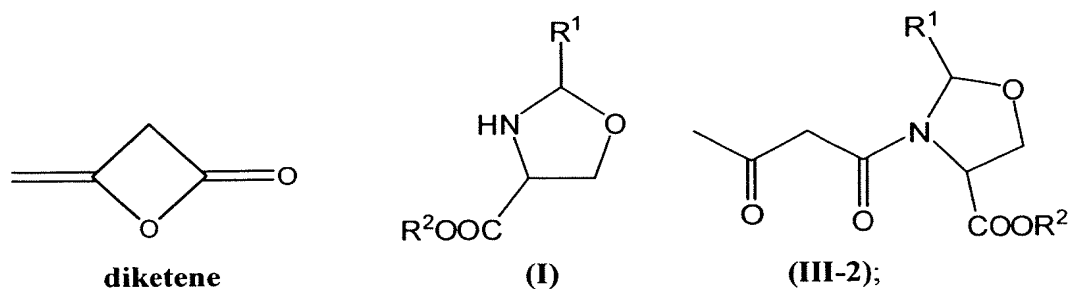


56. The method of any one of Claims 52-55, wherein the compound of formula (VI) has the structure and stereochemistry:

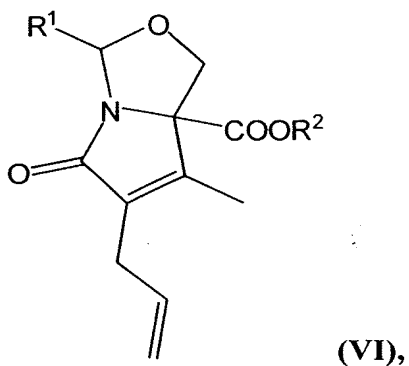


57. The method of any one of Claims 5-37, further comprising:

(a) adding diketene to a compound of formula (I) to form a compound of formula (III-2); and



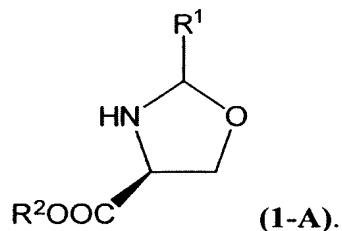
(b) reacting the compound of formula (III-2) with allyl bromide and forming a compound of formula (VI) via an intramolecular aldol condensation reaction:



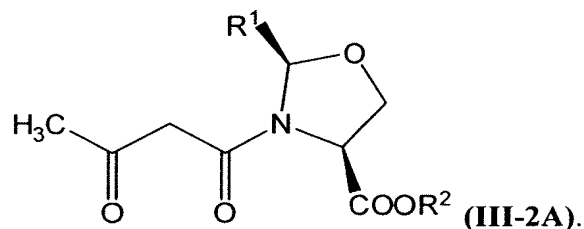
wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or

substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

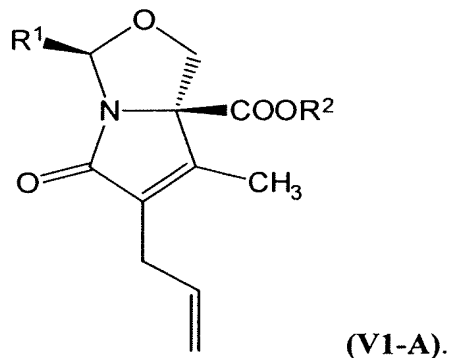
58. The method of Claim 57, wherein the compound of formula (I) has the structure and stereochemistry:



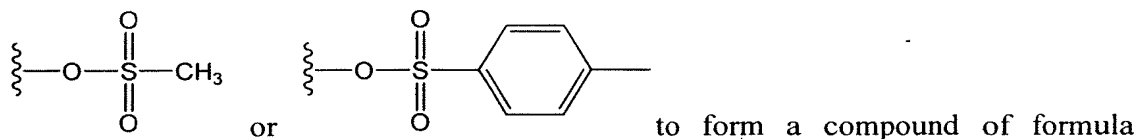
59. The method of any one of Claims 57-58, wherein the compound of formula (III-2) has the structure and stereochemistry:



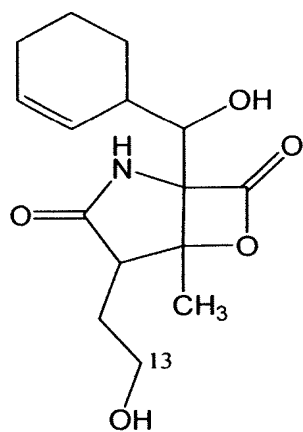
60. The method of any one of Claims 57-59, wherein the compound of formula (VI) has the structure and stereochemistry:



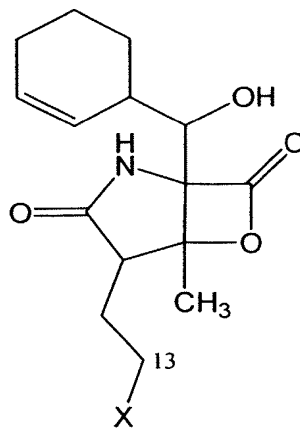
61. The method of any one of Claims 5-60, further comprising replacing the C-13 primary hydroxy group of the compound of formula (XV) with a halogen,



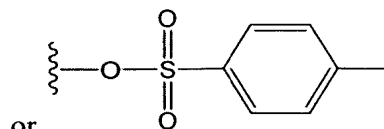
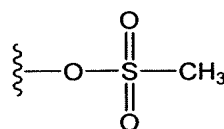
(XVI), wherein the compound of formula (XV) and the compound of formula (XVI) have the following structures:



(XV)



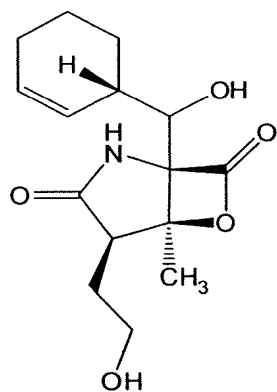
(XVI)



or

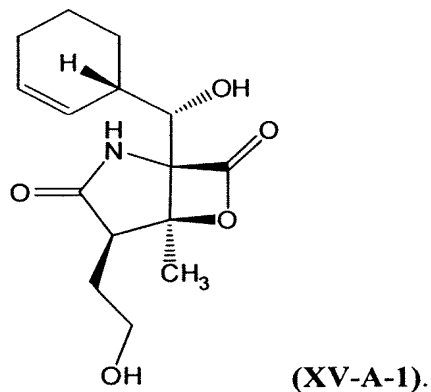
wherein X is a halogen,

62. The method of Claim 61, wherein the compound of formula (XV) has the structure:

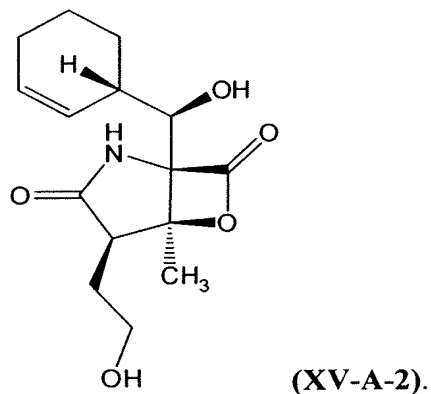


(XV-A).

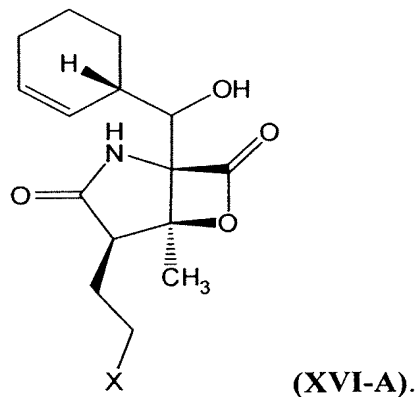
63. The method of Claim 61, wherein the compound of formula (XV) has the structure:



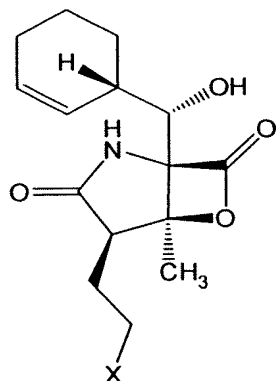
64. The method of Claim 61, wherein the compound of formula (XV) has the structure:



65. The method of any one of Claims 61-64, wherein the compound of formula (XVI) has the structure:

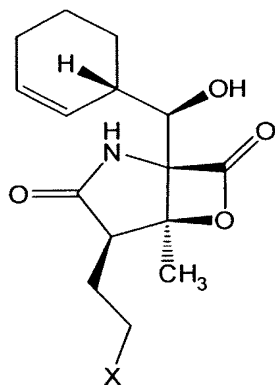


66. The method of any one of Claims 61-64, wherein the compound of formula (XVI) has the structure:



(XVI-A-1).

67. The method of any one of Claims 61-64, wherein the compound of formula (XVI) has the structure:

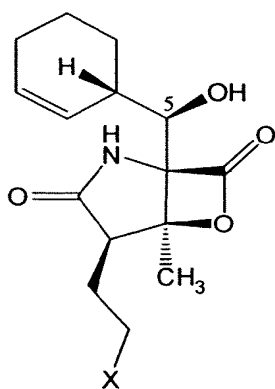


(XVI-A-2).

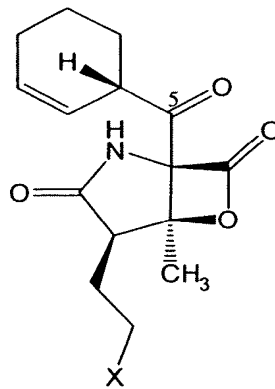
68. The method of any one of Claims 61-67, wherein X is chlorine.

69. The method of Claim 67, further comprising the steps of:

(1) oxidizing the C-5 secondary hydroxyl group of the compound of formula (XVI-A-2) to form a compound of formula (XVIII-A)

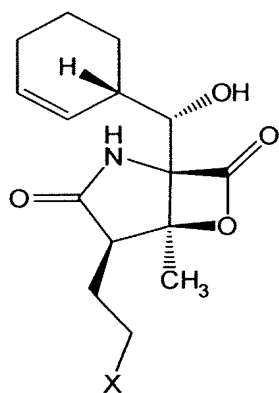


(XVI-A-2)



(XVIII-A); and

(2) reducing the keto group attached to C-5 of the compound of formula (XVIII-A) to form a compound of formula (XVI-A-1)



(XVI-A-1).

70. The method of any one of Claims 12-18, wherein PG¹ is selected from the group consisting of a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylalkylcarbonyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted aryloxy carbonyl, a substituted methyl ether, a substituted ethyl ether; a substituted or substituted benzyl, a tetrahydropyranyl ether; a silyl ether, an ester, a carbonate, and a sulfonate.

71. The method of any one of Claims 12-18, wherein PG¹ is an unsubstituted benzyl or a substituted benzyl.

72. The method of any one of Claims 12-34, wherein PG² is selected from the group consisting of a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylalkylcarbonyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted

aryloxycarbonyl, a substituted methyl ether, a substituted ethyl ether; a substituted or substituted benzyl, a tetrahydropyranyl ether; a silyl ether, an ester, a carbonate, and a sulfonate.

73. The method of any one of Claims 12-34, wherein PG² is an unsubstituted benzyl or a substituted benzyl.

74. The method of any one of Claims 12-18, wherein PG³ is selected from the group consisting of a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylalkylcarbonyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted aryloxycarbonyl, a substituted methyl ether, a substituted ethyl ether; a substituted or substituted benzyl, a tetrahydropyranyl ether; a silyl ether, an ester, a carbonate, and a sulfonate.

75. The method of any one of Claims 12-18, wherein PG³ is an unsubstituted benzyl or a substituted benzyl.

76. The method of any one of Claims 27-34, wherein PG⁴ is selected from the group consisting of a substituted or unsubstituted arylcarbonyl, a substituted or unsubstituted alkylcarbonyl, a substituted or unsubstituted arylalkylcarbonyl, a substituted or unsubstituted alkoxycarbonyl, a substituted or unsubstituted aryloxycarbonyl, a substituted methyl ether, a substituted ethyl ether; a substituted or substituted benzyl, a tetrahydropyranyl ether; a silyl ether, an ester, a carbonate, and a sulfonate.

77. The method of any one of Claims 27-34, wherein PG⁴ is an unsubstituted benzyl or a substituted benzyl.

78. The method of any one of Claims 12-77, wherein:

the organometallic moiety is selected from the group consisting of (2-cyclohexenyl)-MgR⁴, (2-cyclohexenyl)-ZnR⁴, 2-cyclohexenyl-Li, (2-cyclohexenyl)_p-B(R⁴)_{3-p}, and (2-cyclohexenyl)_q-Sn(R⁴)_{4-q};

R⁴ is selected from the group consisting of halogen, or substituted or unsubstituted variants of the following: alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, isopinocampheyl, hydroxy, alkoxy, and carbonylalkoxy, wherein if more than one

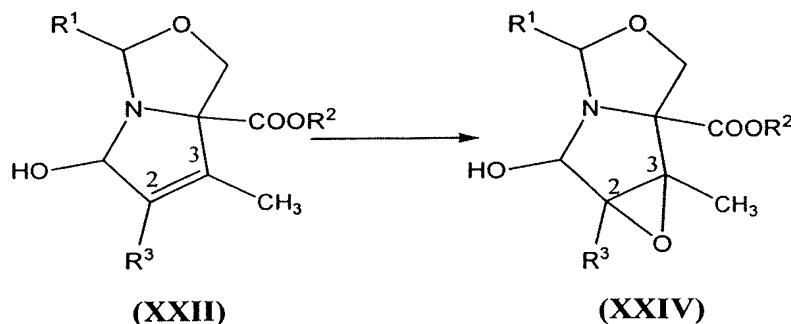
R^4 is present, the R^4 groups can optionally be bond together to form an optionally substituted cycloalkyl, cycloalkenyl, heteroalkyl or heteroalkenyl ring;

p is an integer from 1 to 3; and

q is an integer from 1 to 4.

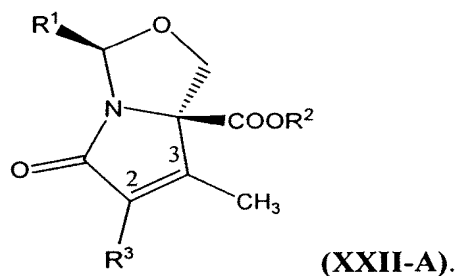
79. The method of Claim 78, wherein the organometallic moiety is (2-cyclohexenyl)-ZnCl.

80. A method of forming a compound of formula (XXIV) comprising oxidizing a compound of formula (XXII) to form a compound of formula (XXIV):

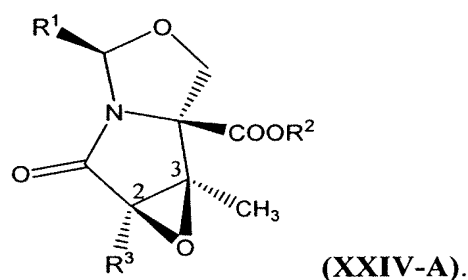


wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; and R^3 is selected from the group consisting of an unsubstituted or substituted C_{1-24} alkyl, an unsubstituted or substituted C_{1-24} alkenyl, an unsubstituted or substituted C_{1-24} alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C_{3-24} cycloalkyl, an unsubstituted or substituted C_{3-24} cycloalkenyl, an unsubstituted or substituted C_{3-24} cycloalkynyl, an unsubstituted or substituted aryl(C_{1-6} alkyl) and an unsubstituted or substituted heteroaryl(C_{1-6} alkyl).

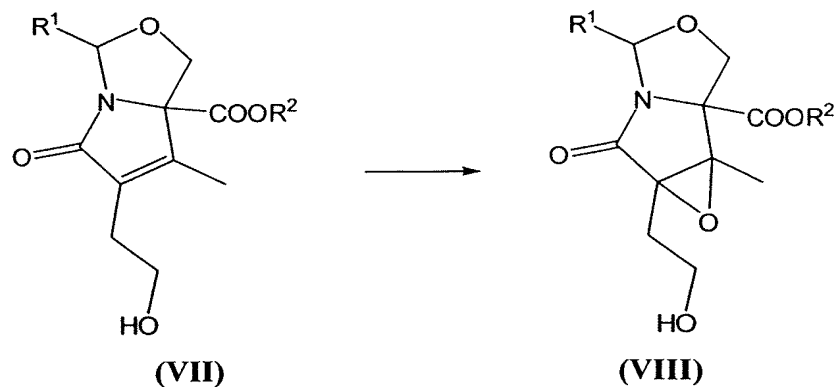
81. The method of Claim 80, wherein the compound of formula (XXII) has the structure and stereochemistry:



82. The method of any one of Claims 80-81, wherein the compound of formula (XXIV) has the structure and stereochemistry:

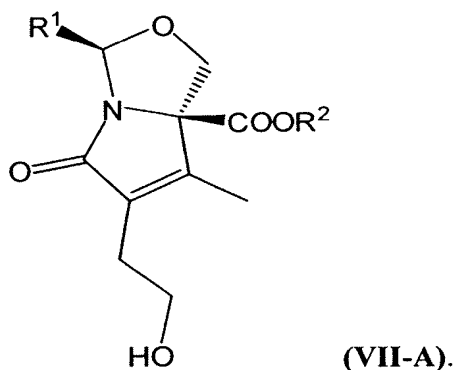


83. A method of forming a compound of formula (VIII) comprising oxidizing a compound of formula (VII) to form a compound of formula (VIII):

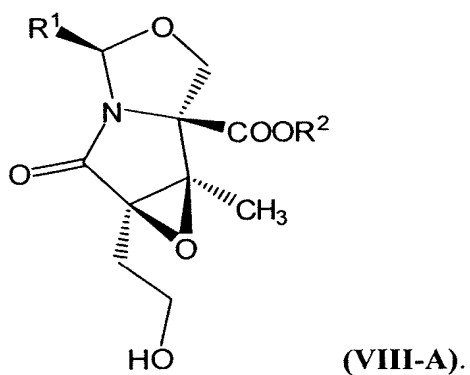


wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

84. The method of Claim 83, wherein the compound of formula (VII) has the structure and stereochemistry:



85. The method of any one of Claims 83-84, wherein the compound of formula (VIII) has the structure and stereochemistry:

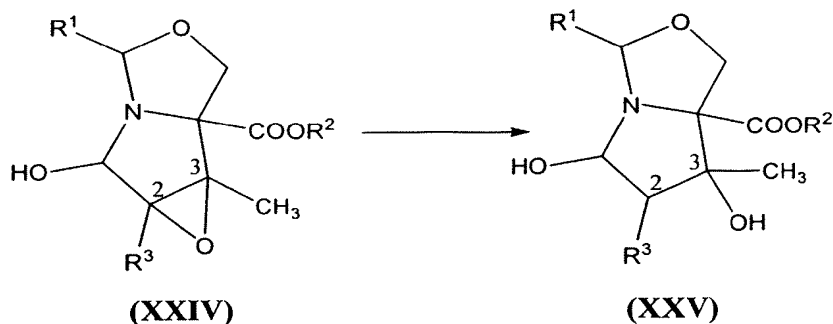


86. The method of any one of Claims 80-85, wherein the epoxide is formed stereoselectively.

87. The method of any one of Claims 80-86, wherein the epoxide is formed using a peroxide.

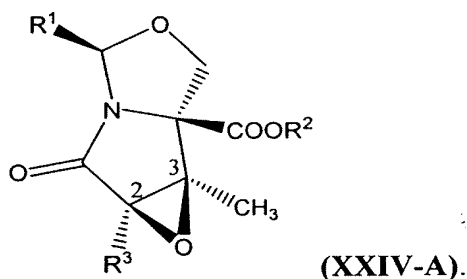
88. The method of Claim 87, wherein the peroxide is tert-butyl hydroperoxide.

89. A method of forming a compound of formula (XXV) comprising cleaving the epoxide of a compound of formula (XXIV) to form a compound of formula (XXV).

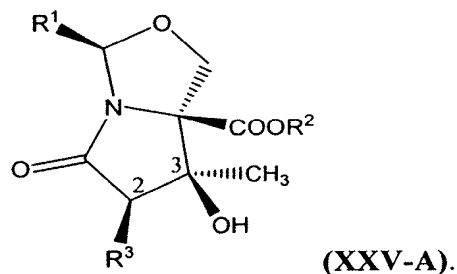


wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; and R^3 is selected from the group consisting of an unsubstituted or substituted C_{1-24} alkyl, an unsubstituted or substituted C_{1-24} alkenyl, an unsubstituted or substituted C_{1-24} alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C_{3-24} cycloalkyl, an unsubstituted or substituted C_{3-24} cycloalkenyl, an unsubstituted or substituted C_{3-24} cycloalkynyl, an unsubstituted or substituted aryl(C_{1-6} alkyl) and an unsubstituted or substituted heteroaryl(C_{1-6} alkyl).

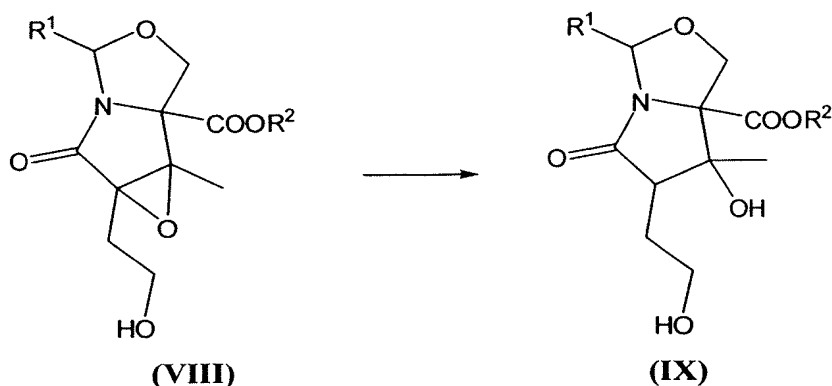
90. The method of Claim 89, wherein the compound of formula (XXIV) has the structure and stereochemistry:



91. The method of any one of Claims 89-90, wherein the compound of formula (XXV) has the structure and stereochemistry:

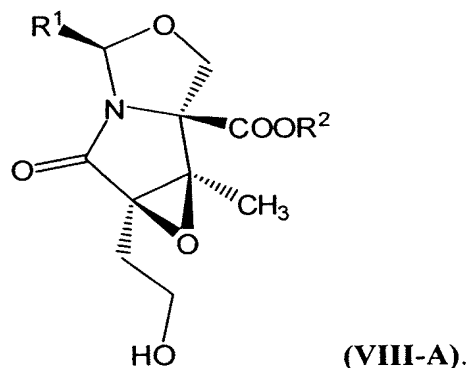


92. A method of forming a compound of formula (IX) comprising cleaving the epoxide of a compound of formula (VIII) to form a compound of formula (IX).

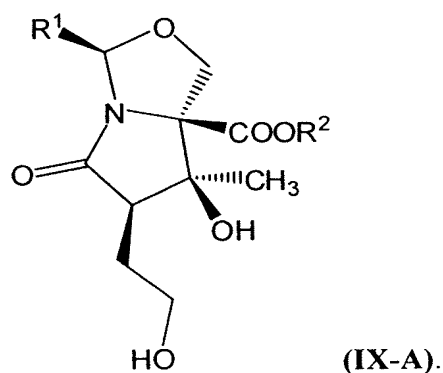


wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

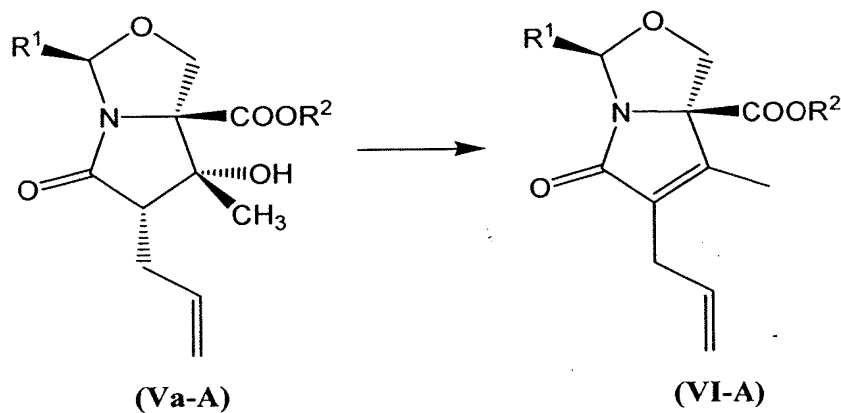
93. The method of Claim 92, wherein the compound of formula (VIII) has the structure and stereochemistry:



94. The method of any one of Claims 92-93, wherein the compound of formula (IX) has the structure and stereochemistry:



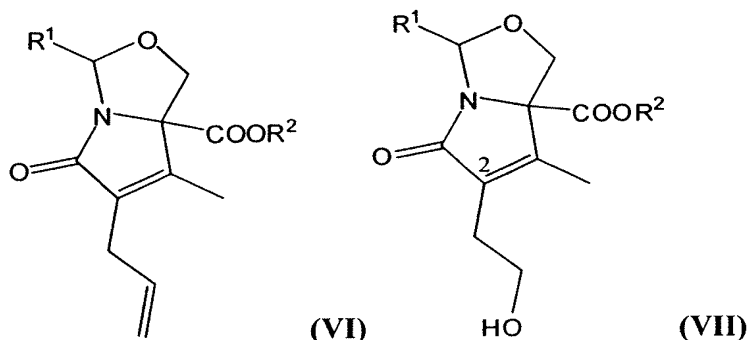
95. A method of preparing a compound of formula (VI-A) comprising a dehydrating a compound of formula (Va-A) to form a compound of formula (VI-A).



wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl;

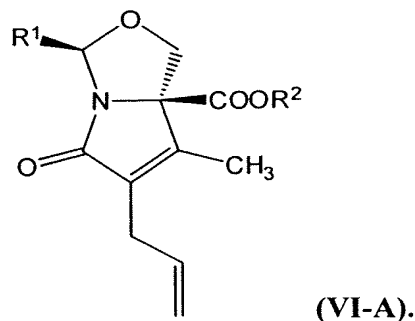
and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

96. A method of preparing a compound of formula (VII) comprising oxidizing the terminal double bond of the allyl substituent at C-2 of a compound of formula (VI) to an aldehyde and reducing the aldehyde to a hydroxy group to form a compound of formula (VII):

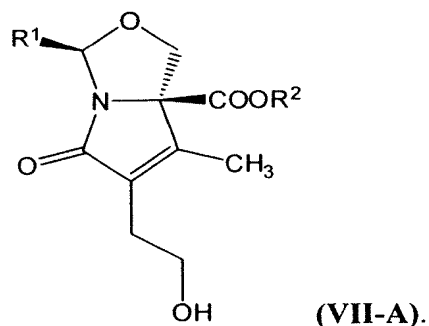


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

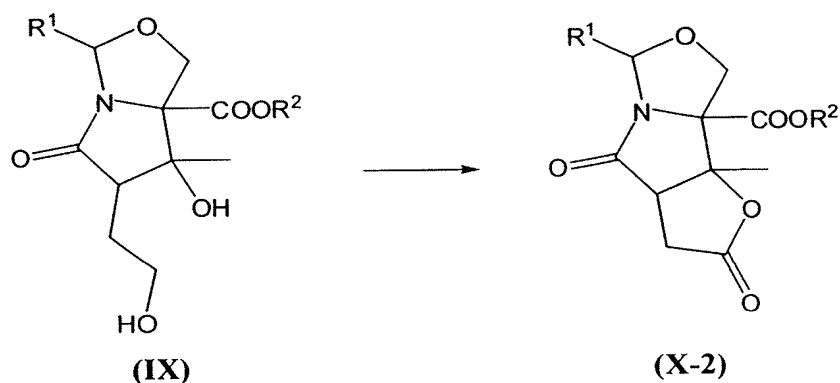
97. The method of Claim 96, wherein the compound of formula (VI) has the structure and stereochemistry:



98. The method of any one of Claims 96-97, wherein the compound of formula (VII) has the structure and stereochemistry:

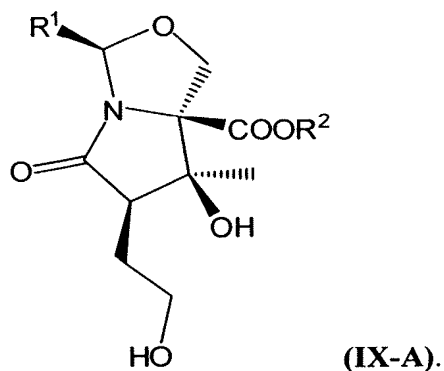


99. A method of preparing a compound of formula (X-2) comprising oxidizing the C-13 primary hydroxy group of the compound of formula (IX) and forming a 5-membered lactone via an intramolecular cyclization reaction.

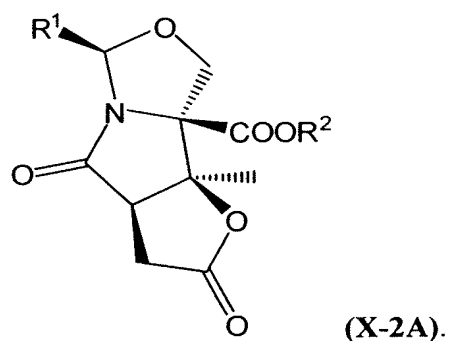


wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

100. The method of Claim 96, wherein the compound of formula (IX) has the structure and stereochemistry:

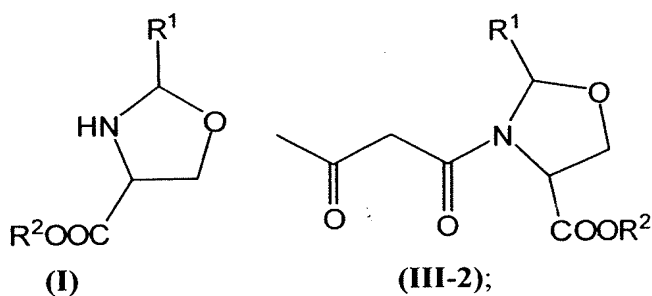


101. The method of any one of Claims 96-100, wherein the compound of formula (X-2) has the structure and stereochemistry:

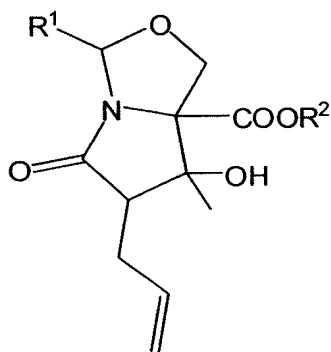


102. A method of preparing a compound of formula (VI) comprising:

(a) reacting acetoacetic acid with a compound of formula (I) to form a compound of formula (III-2):

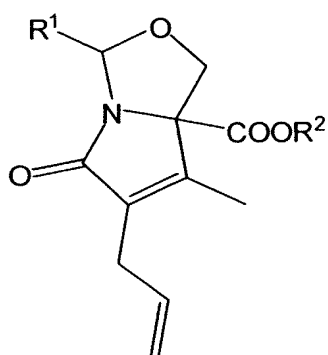


(b) alkylating the compound of formula (III-2) with allyl bromide and forming a compound of formula (V) via an intramolecular aldol reaction:



(V); and

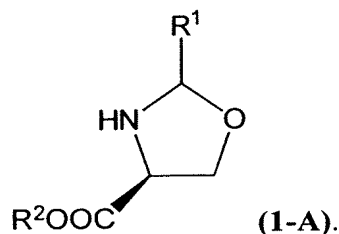
(c) dehydrating the compound of formula (V) to form a double bond between C-2 and C-3 and give a compound of formula (VI):



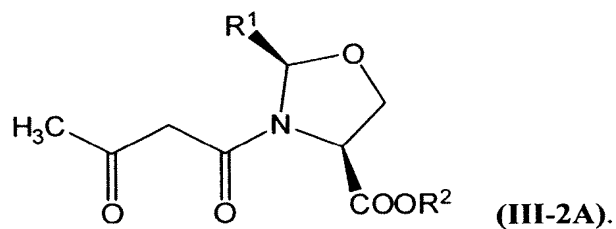
(VI),

wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

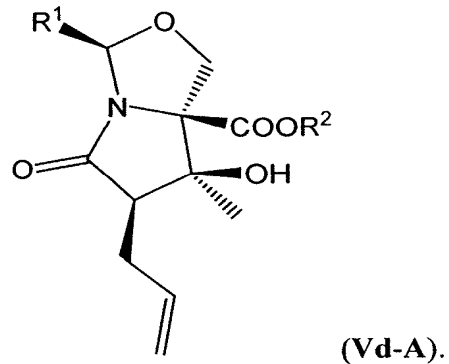
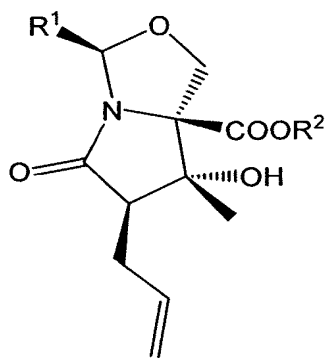
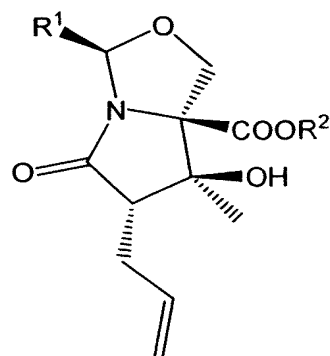
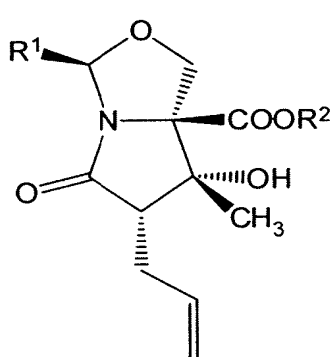
103. The method of Claim 102, wherein the compound of formula (I) has the structure and stereochemistry:



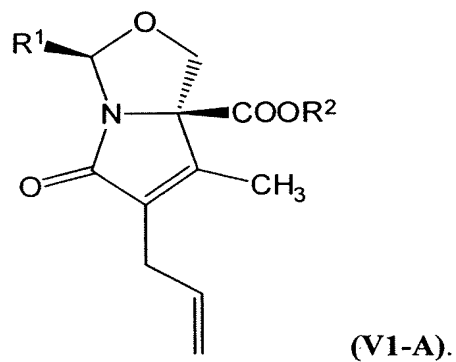
104. The method of any one of Claims 102-103, wherein the compound of formula (III-2) has the structure and stereochemistry:



105. The method of any one of Claims 102-104, wherein the compound of formula (V) has a structure and a stereochemistry selected from the group consisting of:

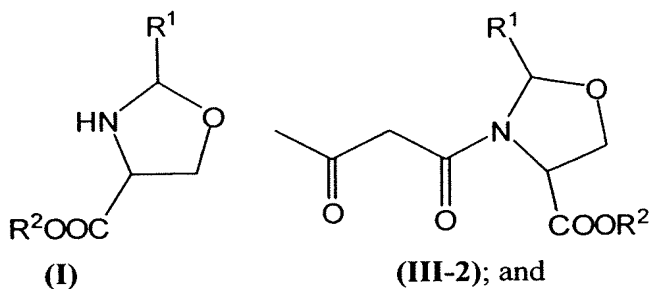


106. The method of any one of Claims 102-105, wherein the compound of formula (VI) has the structure and stereochemistry:

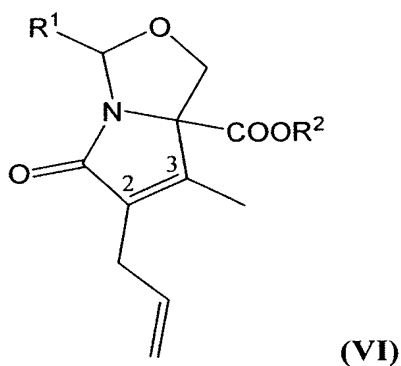


107. A method of preparing a compound of formula (VI) comprising:

(a) reacting acetoacetic acid with a compound of formula (I) to form a compound of formula (III-2); and

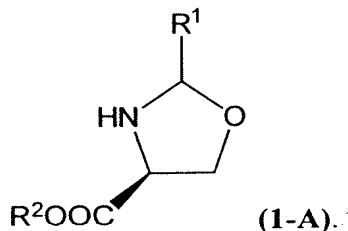


(b) reacting the compound of formula (III-2) with allyl bromide and formingform a compound of formula (VI) via an intramolecular aldol condensation reaction:

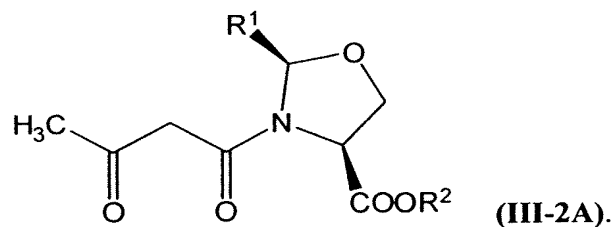


wherein R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

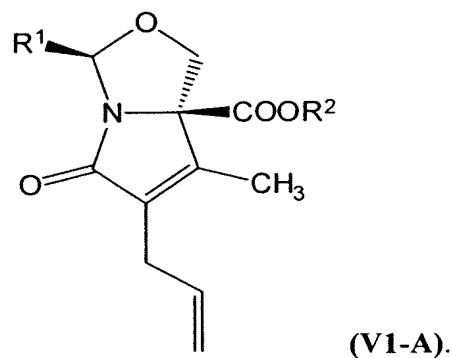
108. The method of Claim 107, wherein the compound of formula (I) has the structure and stereochemistry:



109. The method of any one of Claims 107-108, wherein the compound of formula (III-2) has the structure and stereochemistry:

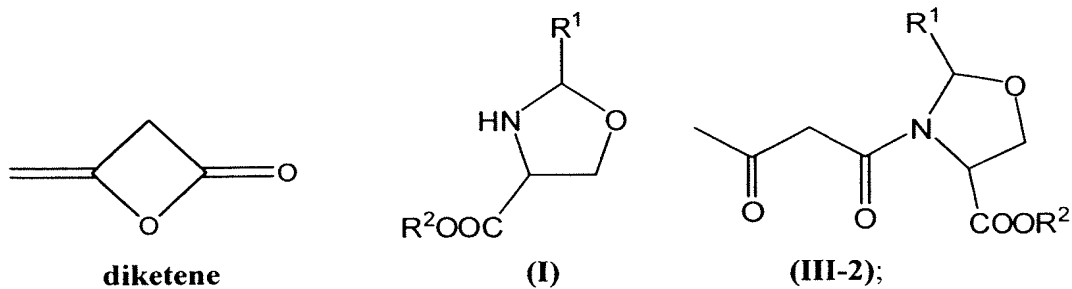


110. The method of any one of Claims 107-109, wherein the compound of formula (VI) has the structure and stereochemistry:

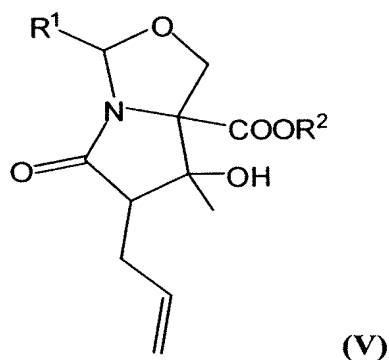


111. A method of preparing a compound of formula (VI) comprising:

(a) adding diketene to a compound of formula (I) to form a compound of formula (III-2);

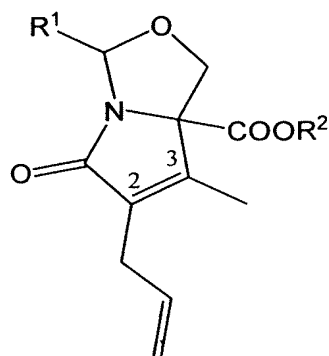


(b) alkylating the compound of formula (III-2) with allyl bromide to form a compound of formula (V) via an intramolecular aldol reaction; and



(V)

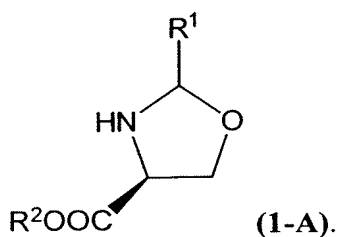
(c) dehydrating the compound of formula (V) to form a compound of formula (VI) to form a double bond between C-2 and C-3 and give a compound of formula (VI):



(VI),

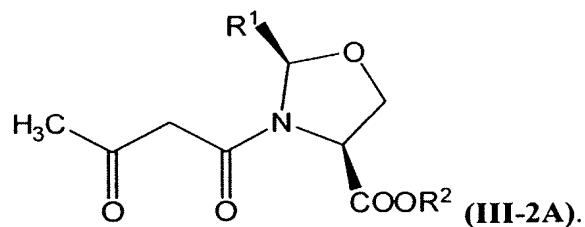
wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; and R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

112. The method of Claim 111, wherein the compound of formula (I) has the structure and stereochemistry:

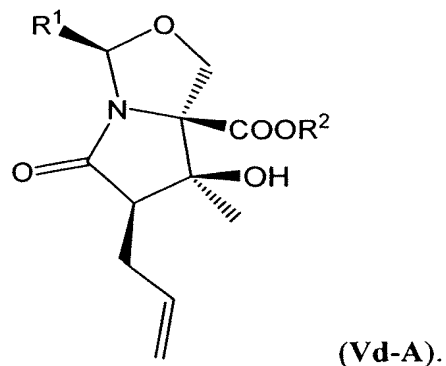
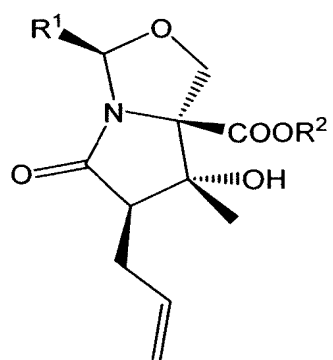
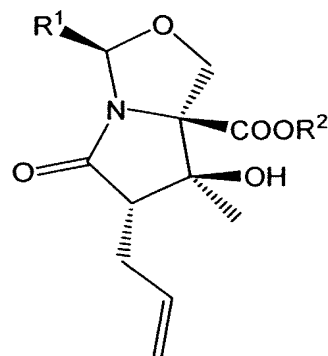
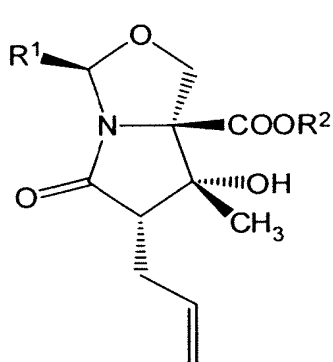


(1-A).

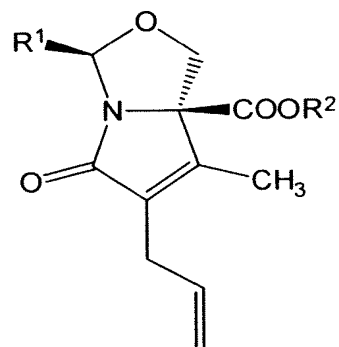
113. The method of any one of Claims 111-112, wherein the compound of formula (III-2) has the structure and stereochemistry:



114. The method of any one of Claims 111-113, wherein the compound of formula (V) has a structure and a stereochemistry selected from the group consisting of:

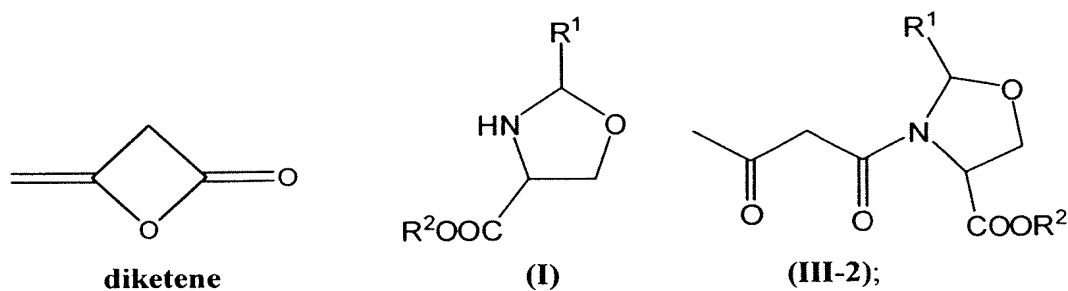


115. The method of any one of Claims 111-114, wherein the compound of formula (VI) has the structure and stereochemistry:

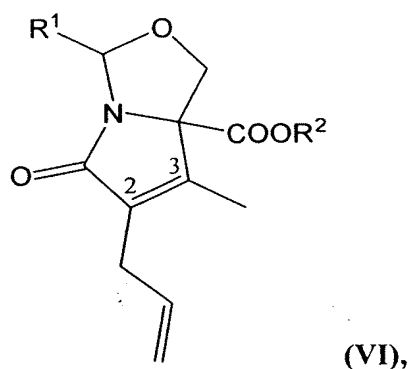


116. A method of preparing a compound of formula (VI) comprising:

(a) adding diketene to a compound of formula (I) to form a compound of formula (III-2); and



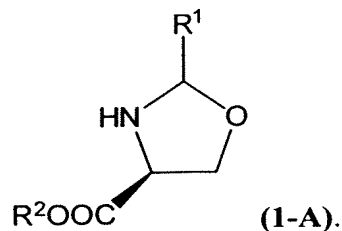
(b) alkylating the compound of formula (III-2) with allyl bromide forming a compound of formula (VI) via an intramolecular aldol condensation reaction:



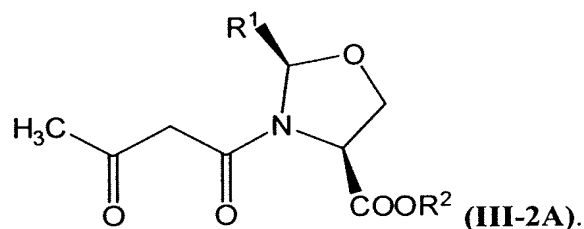
wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or

substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

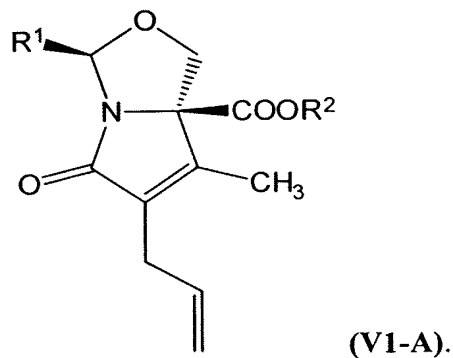
117. The method of Claim 116, wherein the compound of formula (I) has the structure and stereochemistry:



118. The method of any one of Claims 116-117, wherein the compound of formula (III-2) has the structure and stereochemistry:

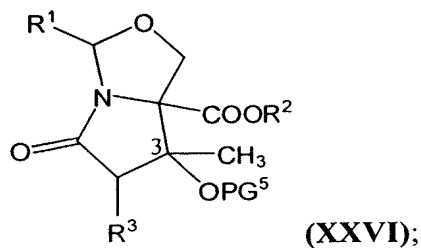


119. The method of any one of Claims 116-118, wherein the compound of formula (VI) has the structure and stereochemistry:

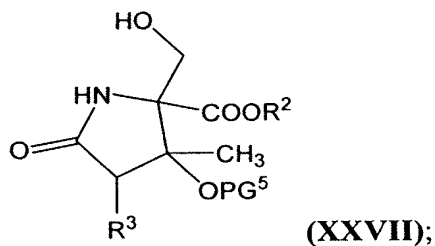


120. The method of Claim 1, further comprising:

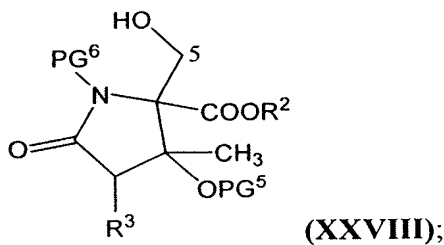
(c) protecting the tertiary alcohol of the compound of formula (XXV) attached to C-3 with an appropriate protecting group to form a compound of formula (XXVI);



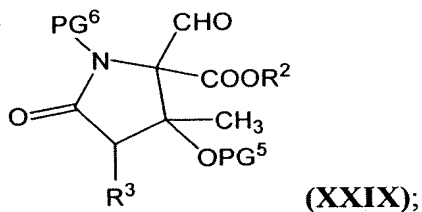
(d) cleaving the aminal group of the compound of formula (XXVI) to form a compound of formula (XXVII):



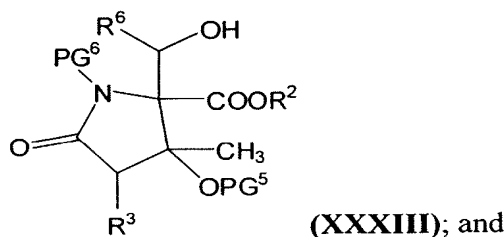
(e) protecting the lactam nitrogen of the compound of formula (XXVII) with PG⁶ to form a compound of formula (XXVIII):



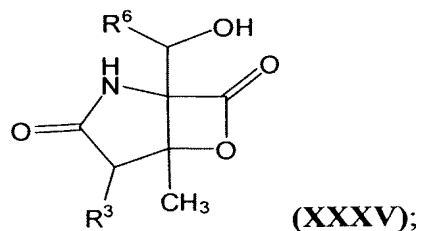
(f) oxidizing the C-5 primary hydroxy group of the compound of formula (XXVIII) to form a compound of formula (XXIX):



(e) reacting the compound of formula (XXIX) with an organometallic moiety that comprises a R⁶ moiety to form a compound of formula (XXXIII):



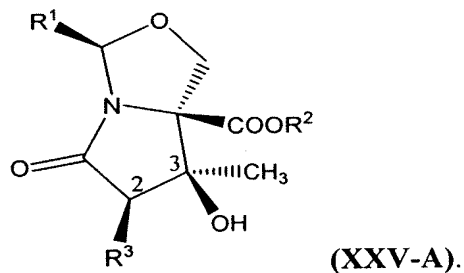
(f) removing PG⁵ and PG⁶ on the compound of formula (XXXIII) and forming a beta-lactone ring to give a compound of formula (XXXV):



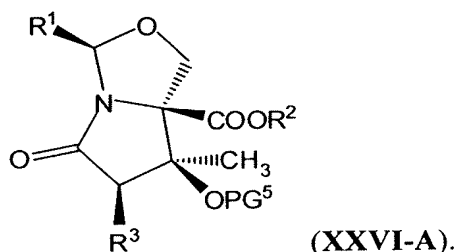
wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; R³ is selected from the group consisting of an unsubstituted or substituted C₁₋₂₄ alkyl, an unsubstituted or substituted C₁₋₂₄ alkenyl, an unsubstituted or substituted C₁₋₂₄ alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C₃₋₂₄ cycloalkyl, an unsubstituted or substituted C₃₋₂₄ cycloalkenyl, an unsubstituted or substituted C₃₋₂₄ cycloalkynyl, an unsubstituted or substituted aryl(C₁₋₆ alkyl) and an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl); R⁶ is selected from the group consisting of an unsubstituted or substituted C_{1-C24} alkyl, an unsubstituted or substituted C_{2-C24} alkenyl, an unsubstituted or substituted C_{2-C24} alkynyl, an unsubstituted or substituted C_{3-C24} cycloalkyl, an unsubstituted or substituted C_{3-C24} cycloalkenyl, an unsubstituted or substituted C_{3-C24} cycloalkynyl, an unsubstituted or substituted heterocyclyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted aryl(C₁₋₆ alkyl), an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl), an unsubstituted or

substituted C₃-C₂₄ cycloalkyl(C₁₋₆ alkyl) and an unsubstituted or substituted heterocyclyl(C₁₋₆ alkyl); and PG⁵ and PG⁶ are each a separate protecting group.

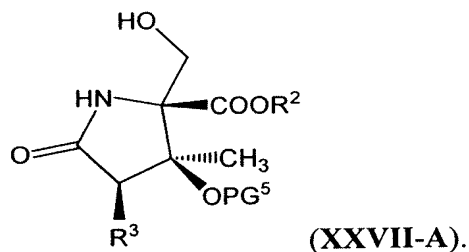
121. The method of Claim 120, wherein the compound of formula (XXV) has the structure and stereochemistry:



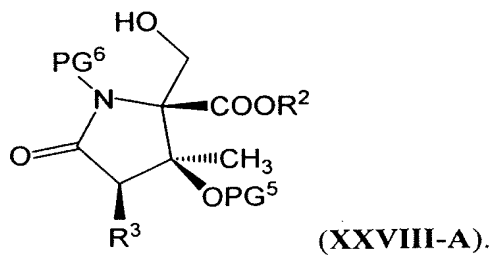
122. The method of any one of Claims 120-121, wherein the compound of formula (XXVI) has the structure and stereochemistry:



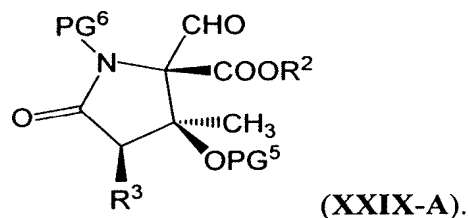
123. The method of any one of Claims 120-122, wherein the compound of formula (XXVII) has the structure and stereochemistry:



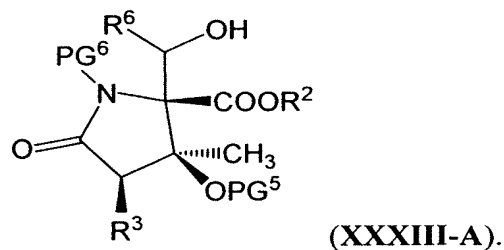
124. The method of any one of Claims 120-123, wherein the compound of formula (XXVIII) has the structure and stereochemistry:



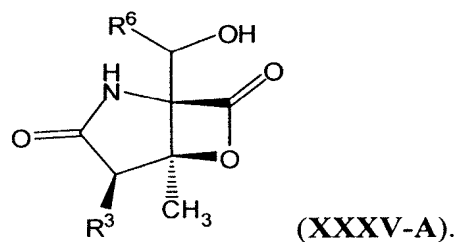
125. The method of any one of Claims 120-124, wherein the compound of formula (XXIX) has the structure and stereochemistry:



126. The method of any one of Claims 120-125, wherein the compound of formula (XXXIII) has the structure and stereochemistry:

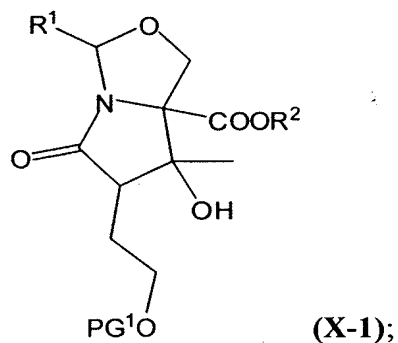


127. The method of any one of Claims 120-126, wherein the compound of formula (XXXV) has the structure and stereochemistry:

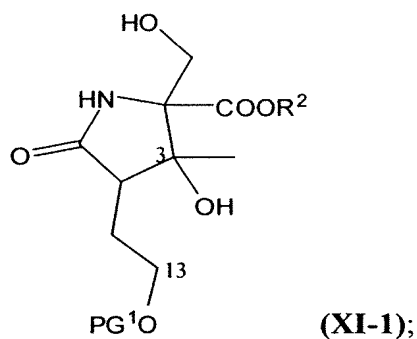


128. The method of any one of Claims 8-11, further comprising:

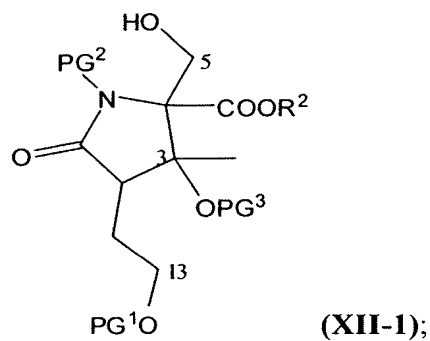
(a) protecting the C-13 primary hydroxy group of the compound of formula (IX) with PG¹ to form a compound of formula (X-1):



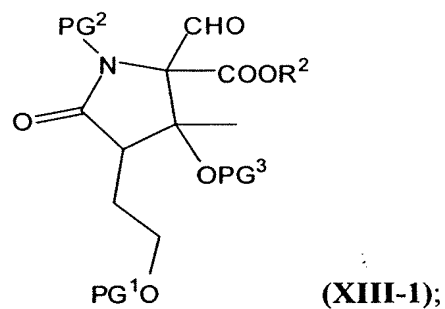
(b) cleaving the aminal group of the compound of formula (X-1) to form a compound of formula (XI-1):



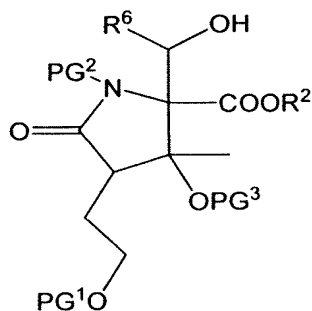
(c) protecting the C-3 tertiary hydroxy group of the compound of formula (XI-1) with PG³ and protecting the lactam nitrogen of the compound of formula (XI-1) with PG² to form a compound of formula (XII-1):



(d) oxidizing the C-5 primary hydroxy group of the compound of formula (XII-1) to form a compound of formula (XIII-1):

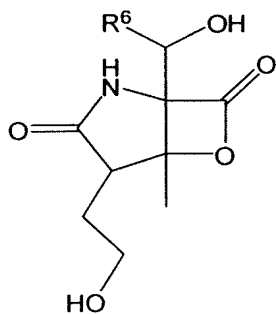


(e) reacting the compound of formula (XIII-1) with an organometallic moiety that comprises a R⁶ moiety to form a compound of formula (XXXII-1):



(XXXII-1); and

(f) removing PG¹, PG² and PG³ from a compound of formula (XXXII-1) and forming a beta-lactone ring to give a compound of formula (XXXIV):

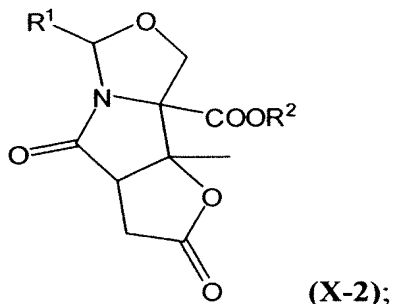


(XXXIV);

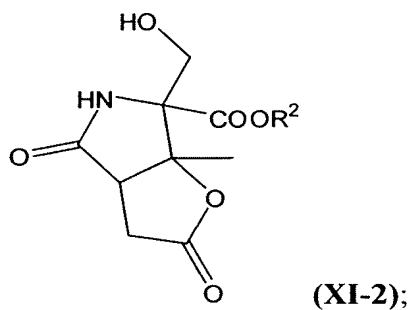
wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; R⁶ is selected from the group consisting of an unsubstituted or substituted C₁₋₂₄ alkyl, an unsubstituted or substituted C₂₋₂₄ alkenyl, an unsubstituted or substituted C₂₋₂₄ alkynyl, an unsubstituted or substituted C₃₋₂₄ cycloalkyl, an unsubstituted or substituted C₃₋₂₄ cycloalkenyl, an unsubstituted or substituted C₃₋₂₄ cycloalkynyl, an unsubstituted or substituted heterocyclyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted aryl(C₁₋₆ alkyl), an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl), an unsubstituted or substituted C₃₋₂₄ cycloalkyl(C₁₋₆ alkyl) and an unsubstituted or substituted heterocyclyl(C₁₋₆ alkyl); and PG¹, PG² and PG³ are each a separate protecting group.

129. The method of any one of Claims 8-11, further comprising:

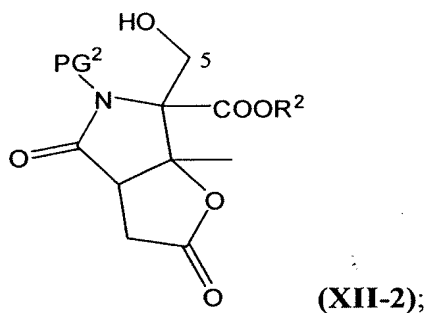
(a) oxidizing the C-13 primary hydroxy group of the compound of formula (IX) and forming a 5-membered lactone via an intramolecular cyclization reaction to give a compound of formula (X-2):



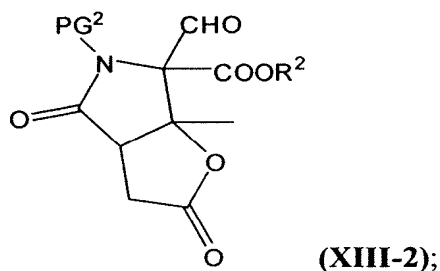
(b) cleaving the aminal group of the compound of formula (X-2) to form a compound of formula (XI-2):



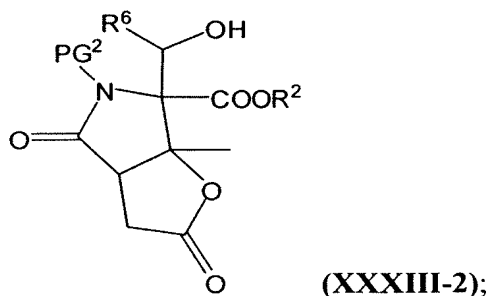
(c) protecting the lactam nitrogen of the compound of formula (XI-2) with PG² to form a compound of formula (XII-2):



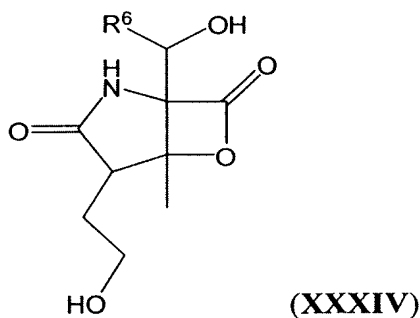
(d) oxidizing the C-5 primary hydroxy group of the compound of formula (XII-2) to form a compound of formula (XIII-2):



(e) reacting the compound of formula (XIII-2) with an organometallic moiety that comprises a R^6 moiety to form a compound of formula (XXXII-2):



(f) cleaving the 5-membered lactone of the compound of formula (XXXII-2), removing PG^2 and forming a beta-lactone ring to give a compound of formula (XXXIV):

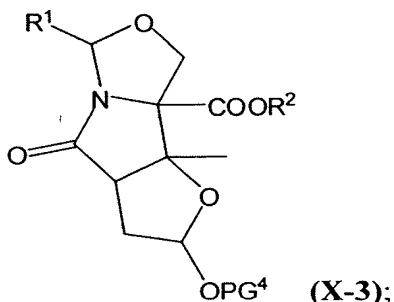


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; R^6 is selected from the group consisting of an unsubstituted or substituted C_{1-24} alkyl, an unsubstituted or substituted C_{2-24} alkenyl, an unsubstituted or substituted C_{2-24} alkynyl, an unsubstituted or substituted C_3-C_{24} cycloalkyl, an unsubstituted or substituted C_3-C_{24} cycloalkenyl, an unsubstituted

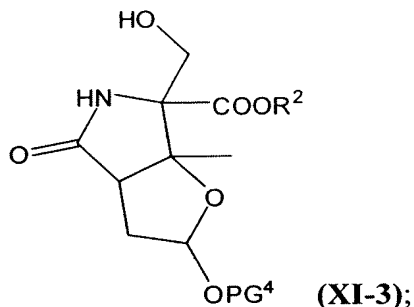
or substituted C₃-C₂₄ cycloalkynyl, an unsubstituted or substituted heterocyclyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted aryl(C₁₋₆ alkyl), an unsubstituted or substituted heteroaryl(C₁₋₆ alkyl), an unsubstituted or substituted C₃-C₂₄ cycloalkyl(C₁₋₆ alkyl) and an unsubstituted or substituted heterocyclyl(C₁₋₆ alkyl); and PG² is a protecting group.

130. The method of any one of Claims 8-11, further comprising:

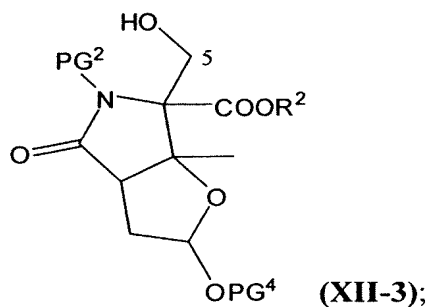
(a) oxidizing the C-13 alcohol to an aldehyde and cyclizing the aldehyde with the C-3 tertiary hydroxy group of the compound of formula (IX) to form a hemi-acetal ring and protecting the secondary hydroxyl group of the hemi-acetal ring to form a compound of formula (X-3):



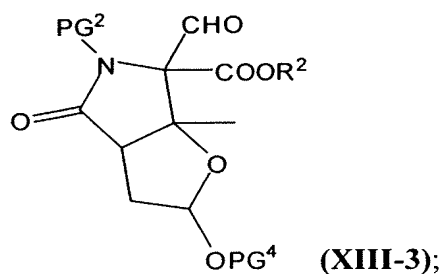
(b) cleaving the aминаl group of the compound of formula (X-3) to form a compound of formula (XI-3):



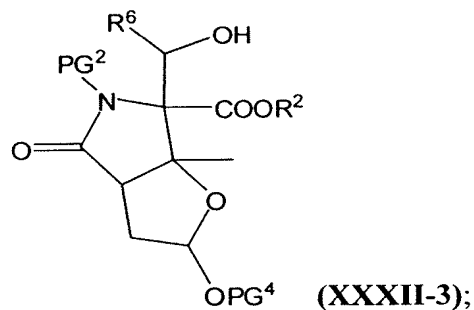
(c) protecting the lactam nitrogen of the compound of formula (XI-3) with PG² to form a compound of formula (XII-3):



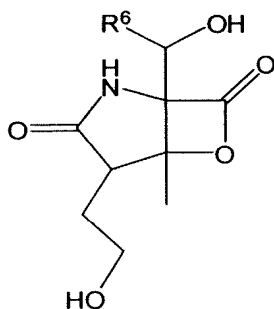
(d) oxidizing the C-5 primary hydroxy group of the compound of formula (XII-3) to form a compound of formula (XIII-3):



(e) reacting the compound of formula (XIII-3) with an organometallic moiety that comprises a R⁶ moiety to form a compound of formula (XXXII-3):



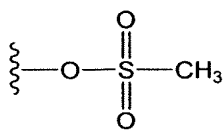
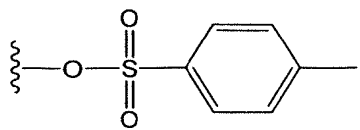
(f) removing the PG⁴ protecting group and cleaving the hemi-acetal ring of the compound of formula (XXXII-3), removing PG² and forming a beta-lactone ring to give a compound of formula (XXXIV):

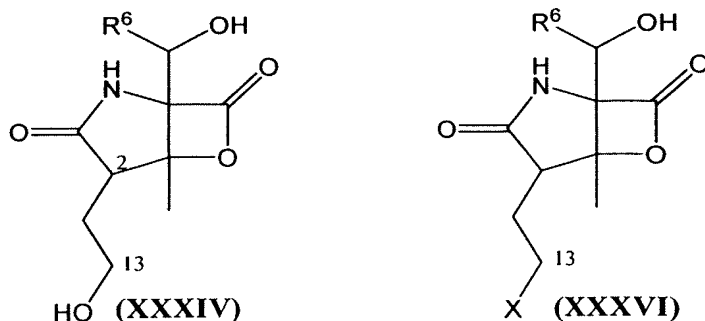


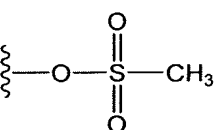
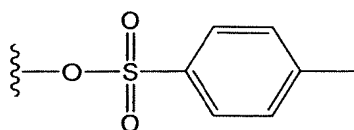
(XXXIV);

wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; R^6 is selected from the group consisting of an unsubstituted or substituted C_1-C_{24} alkyl, an unsubstituted or substituted C_2-C_{24} alkenyl, an unsubstituted or substituted C_2-C_{24} alkynyl, an unsubstituted or substituted C_3-C_{24} cycloalkyl, an unsubstituted or substituted C_3-C_{24} cycloalkenyl, an unsubstituted or substituted C_3-C_{24} cycloalkynyl, an unsubstituted or substituted heterocyclyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted aryl(C_{1-6} alkyl), an unsubstituted or substituted heteroaryl(C_{1-6} alkyl), an unsubstituted or substituted C_3-C_{24} cycloalkyl(C_{1-6} alkyl) and an unsubstituted or substituted heterocyclyl(C_{1-6} alkyl); and PG^2 and PG^4 are each a separate protecting group.

131. The method of any one of Claims 128-130, further comprising replacing the C-13 hydroxy with replacing the C-13 primary hydroxy group of the compound of

formula (XXXIV) with a halogen,  or  to form a compound of formula (XXXVI), wherein the compound of formula (XXXIV) and the compound of formula (XXXVI) have the following structures:



wherein X is a halogen,  or .

132. The method of any one of Claims 120-131, wherein R⁶ is an unsubstituted or substituted C₁₋₂₄ alkyl.

133. The method of Claim 132, wherein R⁶ is isopropyl.

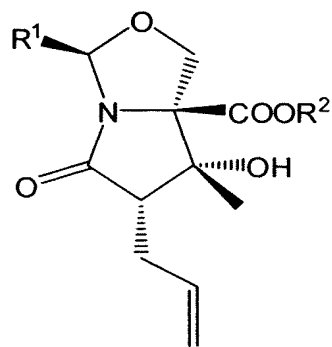
134. The method of any one of Claims 1 to 132, wherein R¹ is an unsubstituted or substituted C₁₋₆ alkyl.

135. The method of Claim 134, wherein R¹ is t-butyl.

136. The method of any one of Claims 1 to 135, wherein R² is an unsubstituted or substituted C₁₋₆ alkyl.

137. The method of Claim 136, wherein R² is methyl.

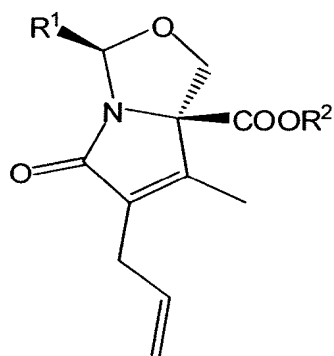
138. A compound of formula (Va-A):



(Va-A).

wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; and R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

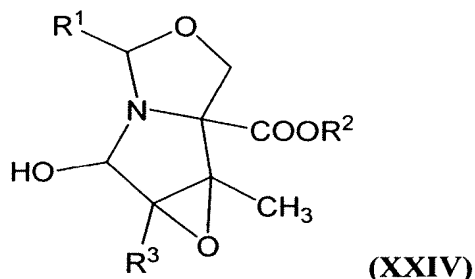
139. A compound of formula (VI-A):



(VI-A).

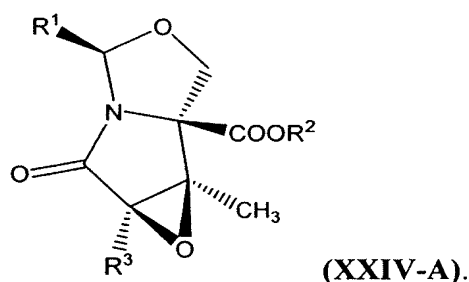
wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; and R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

140. A compound of formula (XXIV):

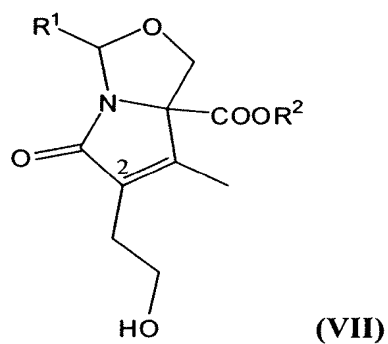


wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl; and R^3 is selected from the group consisting of an unsubstituted or substituted C_{1-24} alkyl, an unsubstituted or substituted C_{1-24} alkenyl, an unsubstituted or substituted C_{1-24} alkynyl, an unsubstituted or substituted aryl, an unsubstituted or substituted heteroaryl, an unsubstituted or substituted C_{3-24} cycloalkyl, an unsubstituted or substituted C_{3-24} cycloalkenyl, an unsubstituted or substituted C_{3-24} cycloalkynyl, an unsubstituted or substituted aryl(C_{1-6} alkyl) and an unsubstituted or substituted heteroaryl(C_{1-6} alkyl).

141. The compound of Claim 140, wherein the compound of formula (XXIV) has the structure and stereochemistry:

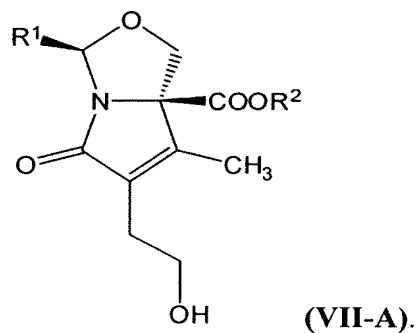


142. A compound of formula (VII):

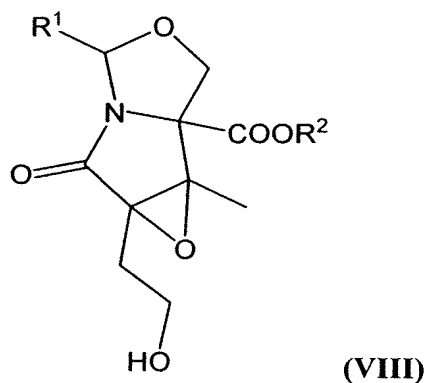


wherein: R¹ is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, and an unsubstituted or substituted aryl; and R² is selected from the group consisting of hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

143. The compound of Claim 142, wherein the compound of formula (VII) has the structure and stereochemistry:

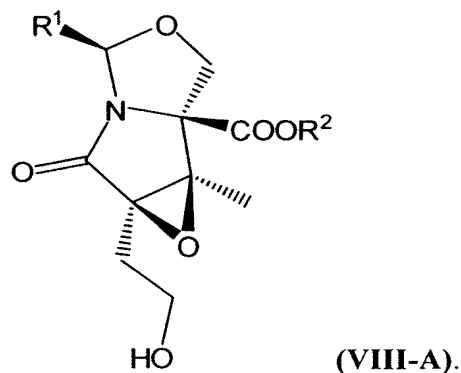


144. A compound of formula (VIII):



wherein: R^1 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, and an unsubstituted or substituted aryl; and R^2 is selected from the group consisting of hydrogen, an unsubstituted or substituted C_{1-6} alkyl, an unsubstituted or substituted aryl, and an unsubstituted or substituted arylalkyl.

145. The compound of Claim 144, wherein the compound of formula (VIII) has the structure and stereochemistry:



146. The compound of any one of Claims 138-145, wherein R^1 is an unsubstituted or substituted C_{1-6} alkyl.

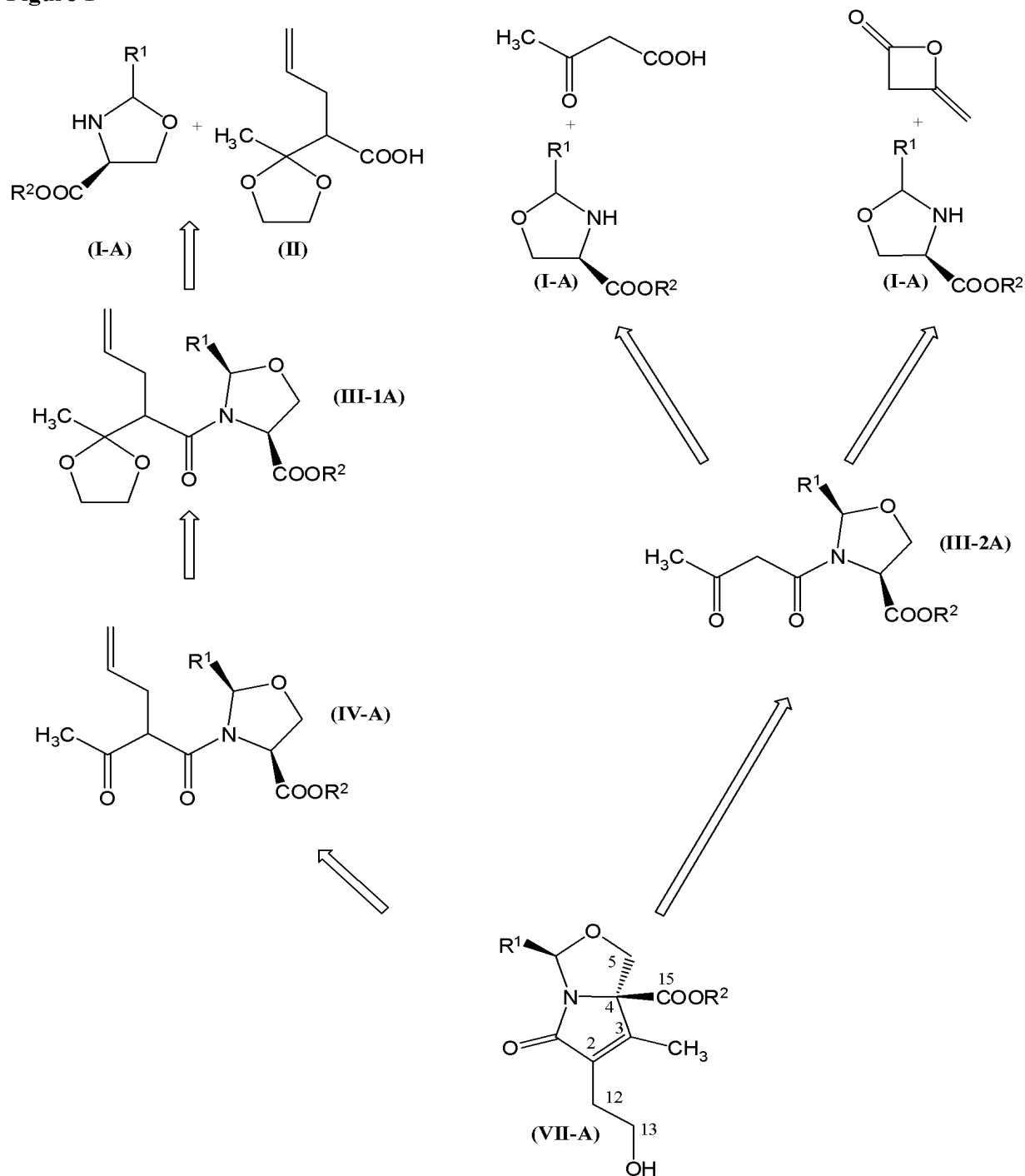
147. The compound of Claim 146, wherein R^1 is t-butyl.

148. The compound of any one of Claims 138-147, wherein R^2 is an unsubstituted or substituted C_{1-6} alkyl.

149. The compound of Claim 148, wherein R^2 is methyl.

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Figure 1

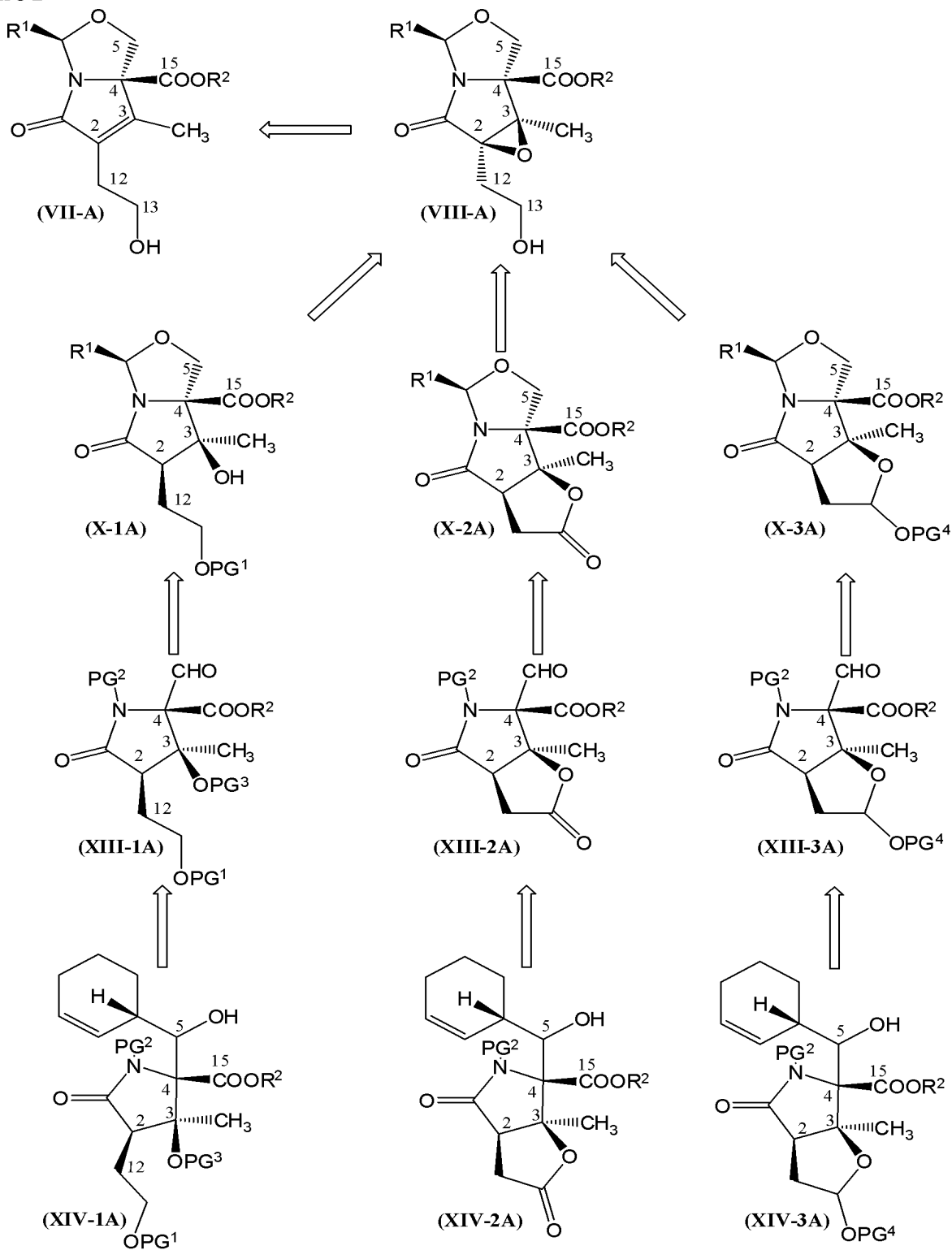


For Schemes 1-4d:

R¹ = hydrogen, unsubstituted or substituted C₁₋₆ alkyl or unsubstituted or substituted aryl; R² = hydrogen, an unsubstituted or substituted C₁₋₆ alkyl, an unsubstituted or substituted aryl, or an unsubstituted or substituted arylalkyl.

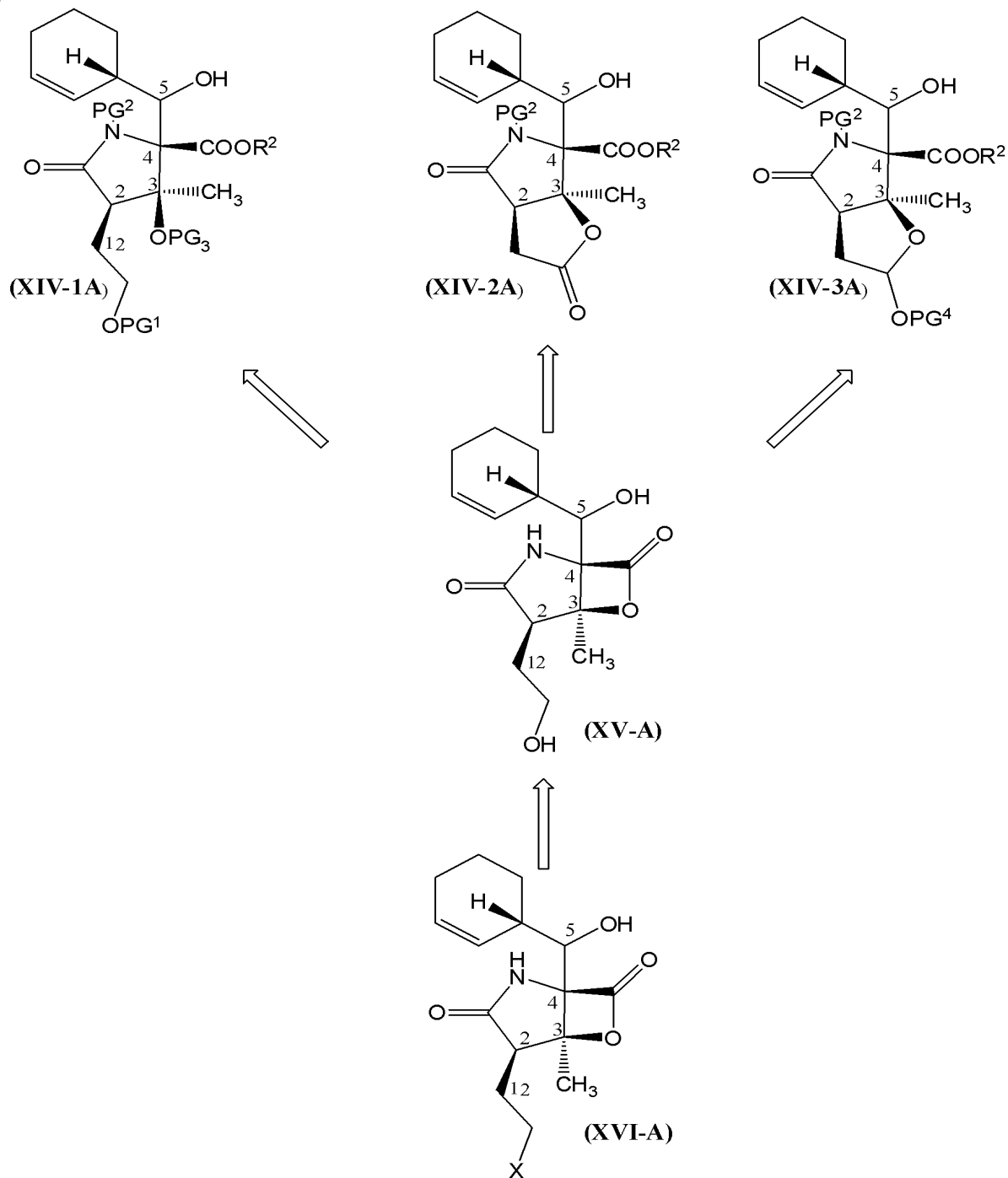
2/47

Figure 2



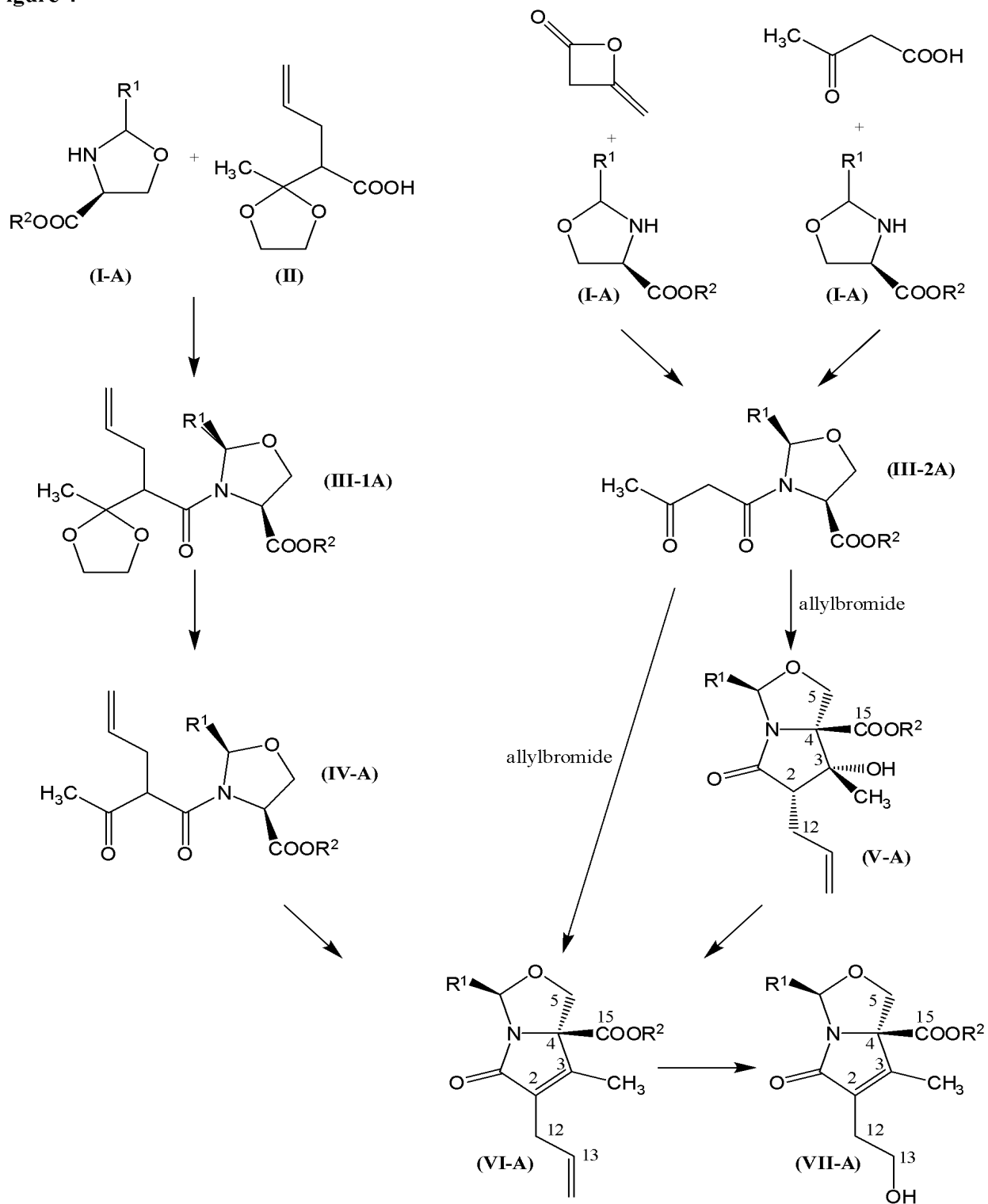
3/47

Figure 3



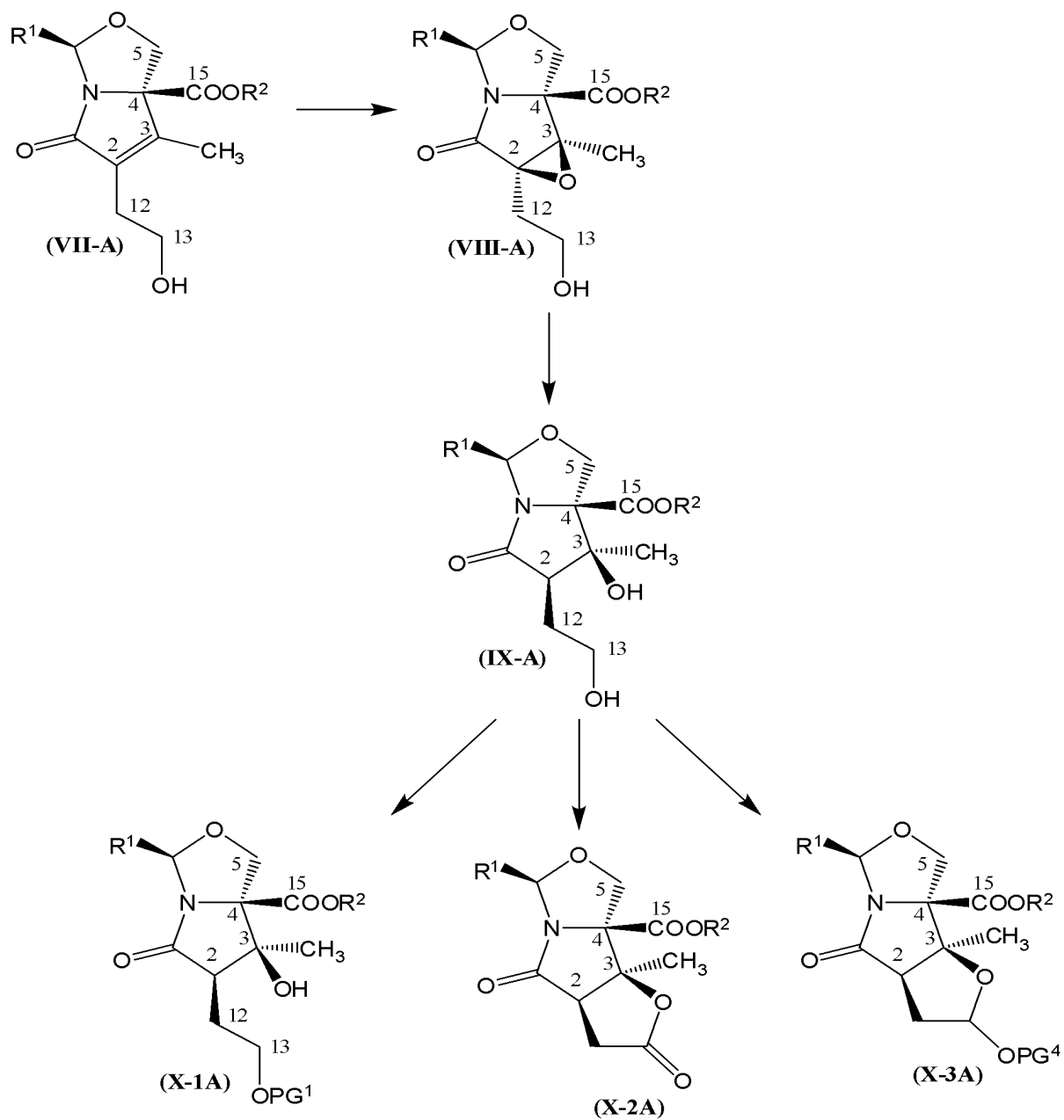
4/47

Figure 4



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Figure 4a



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Figure 4b

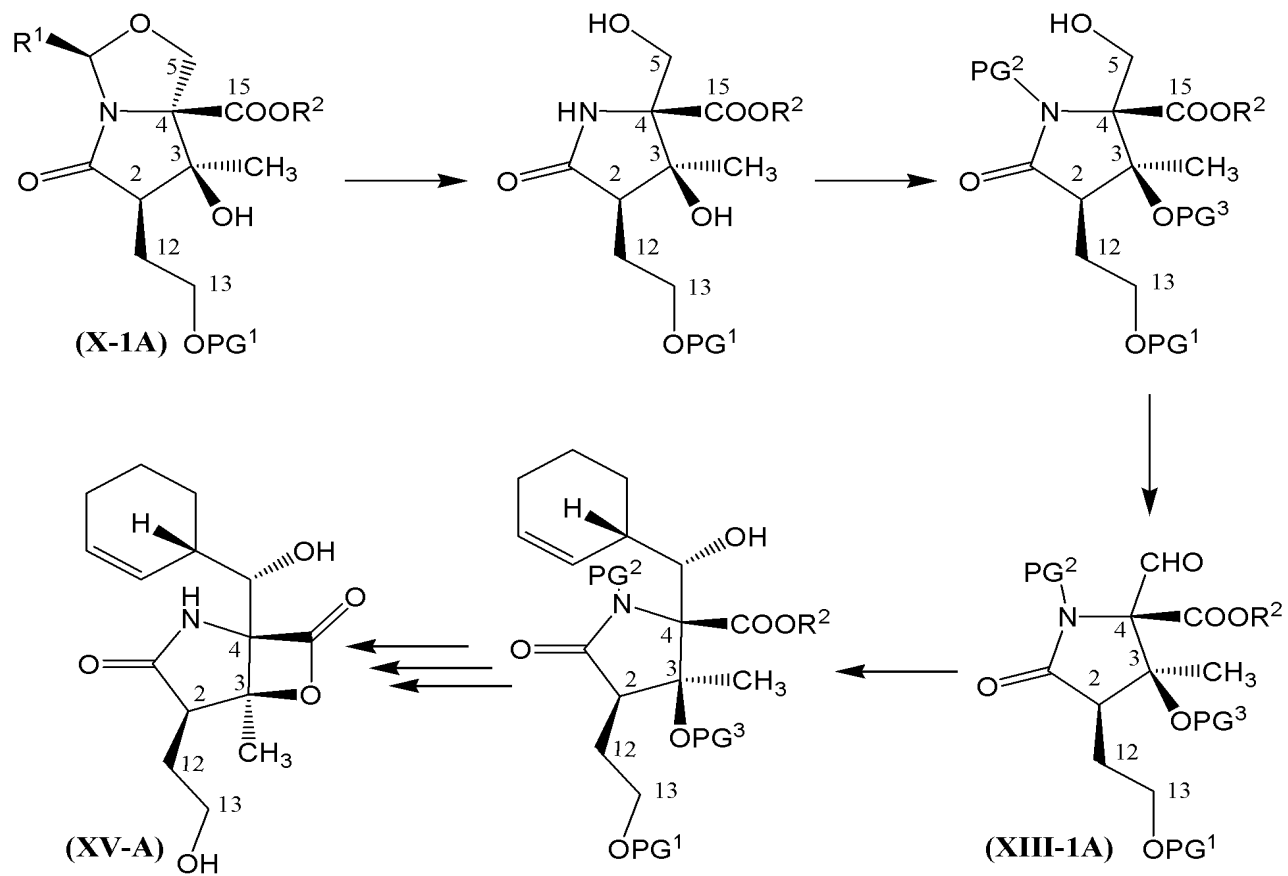


Figure 4c

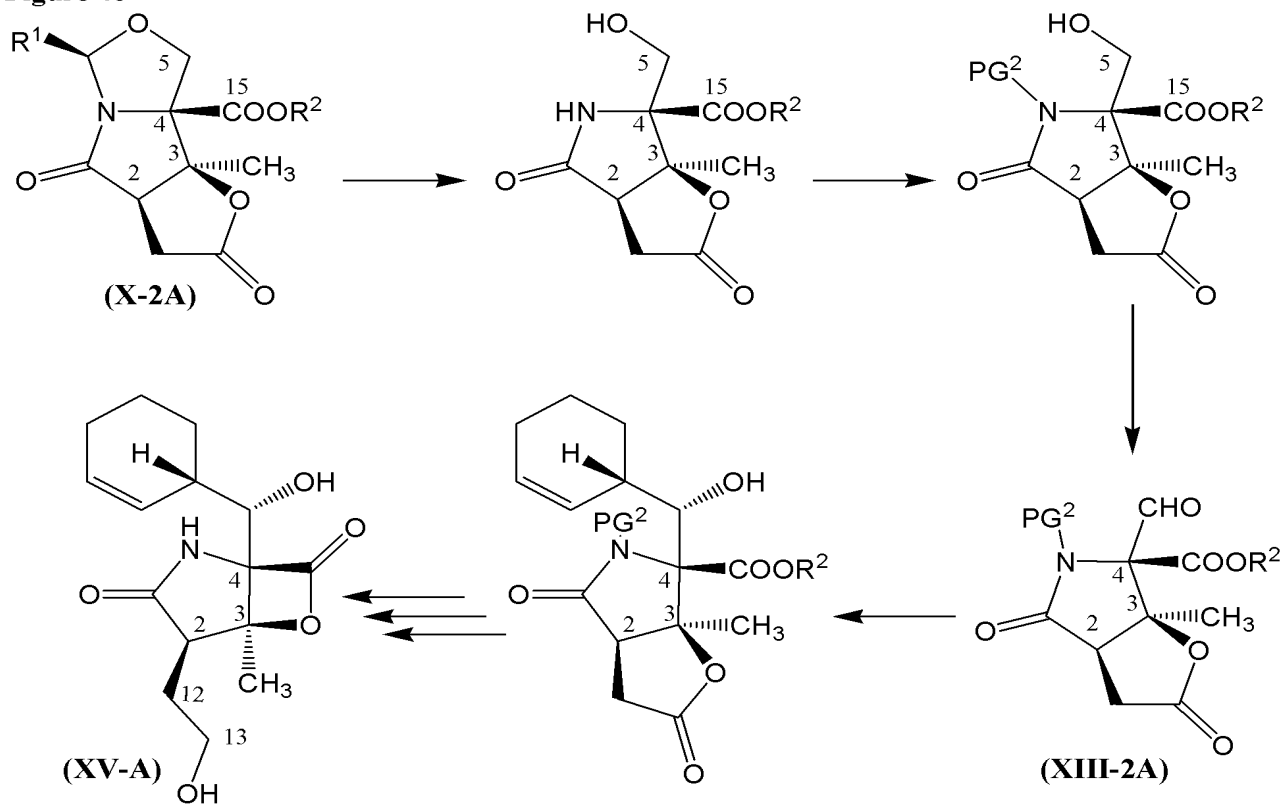


Figure 4d

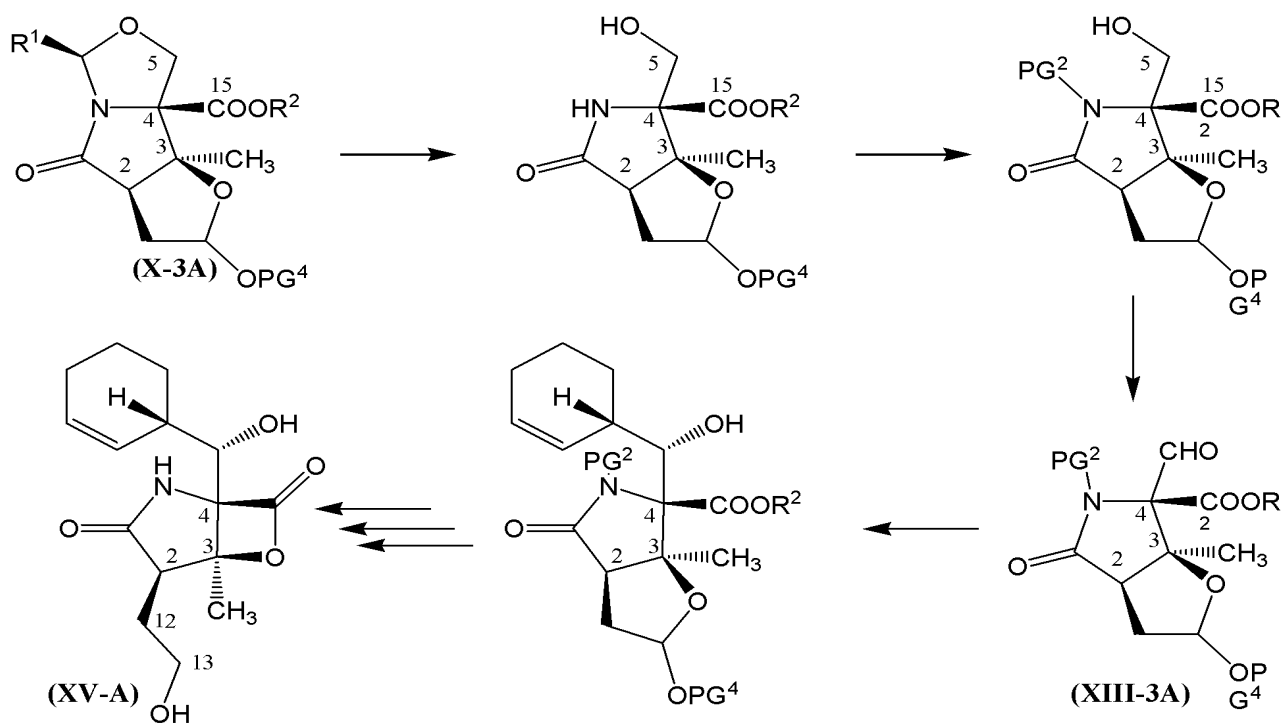
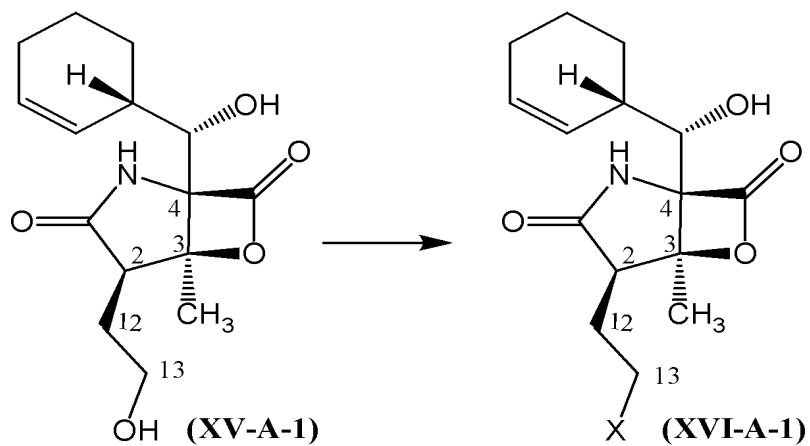
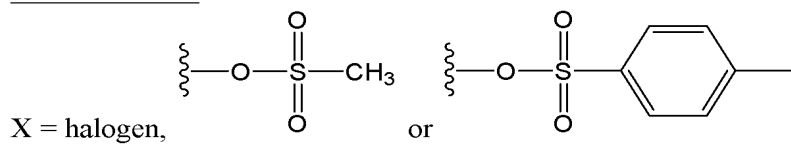


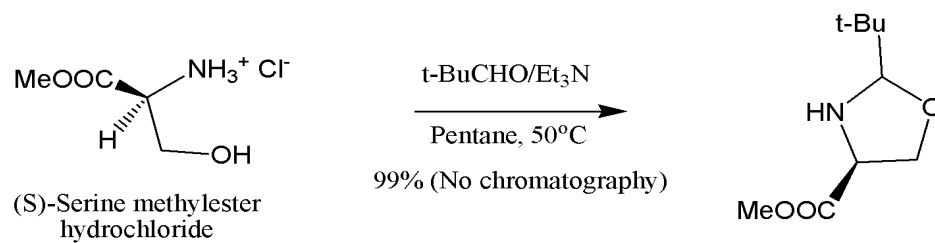
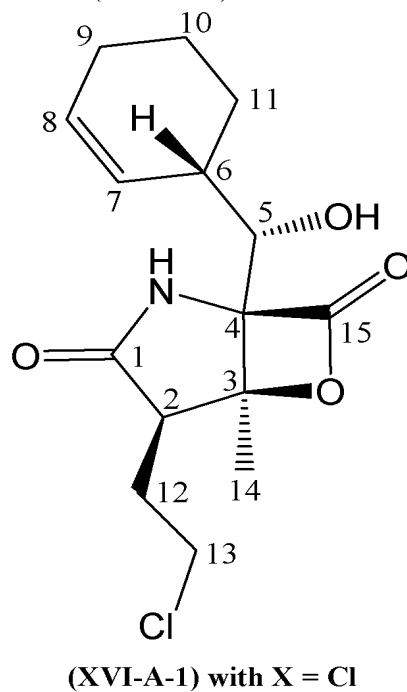
Figure 4e



For Scheme 4e:



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Figure 5**Figure 6.** Structure of Salinosporamide A (NPI-0052)

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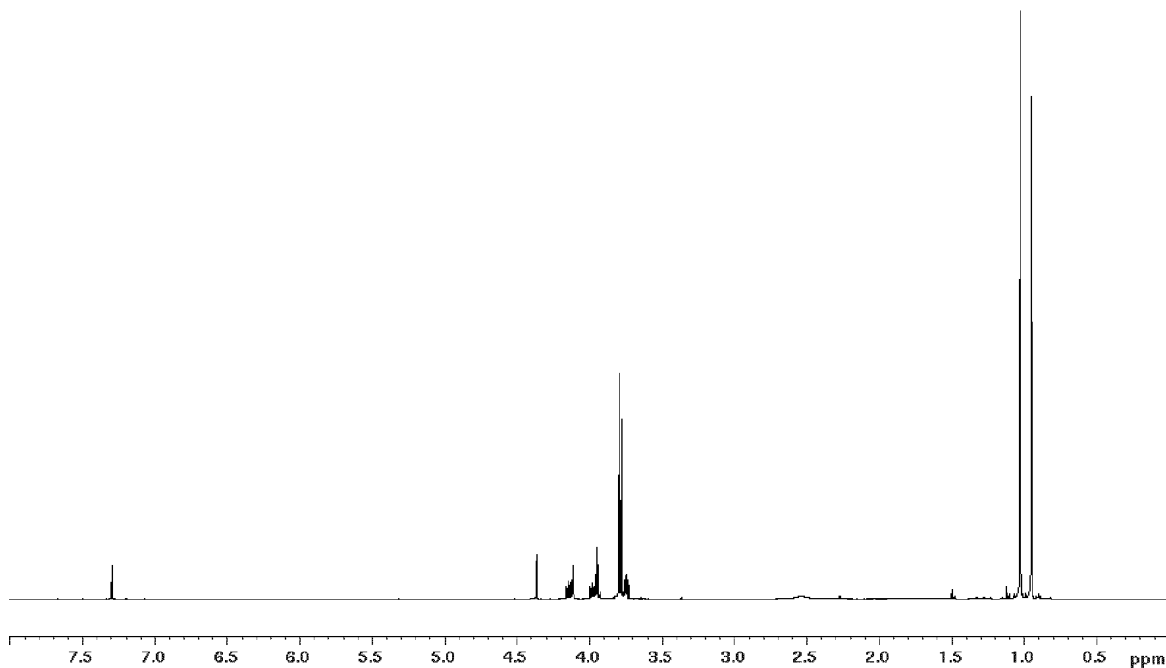


Fig-7: ¹H-NMR of Compound (I-B) (R^1 = t-butyl and R^2 = methyl) in CDCl₃

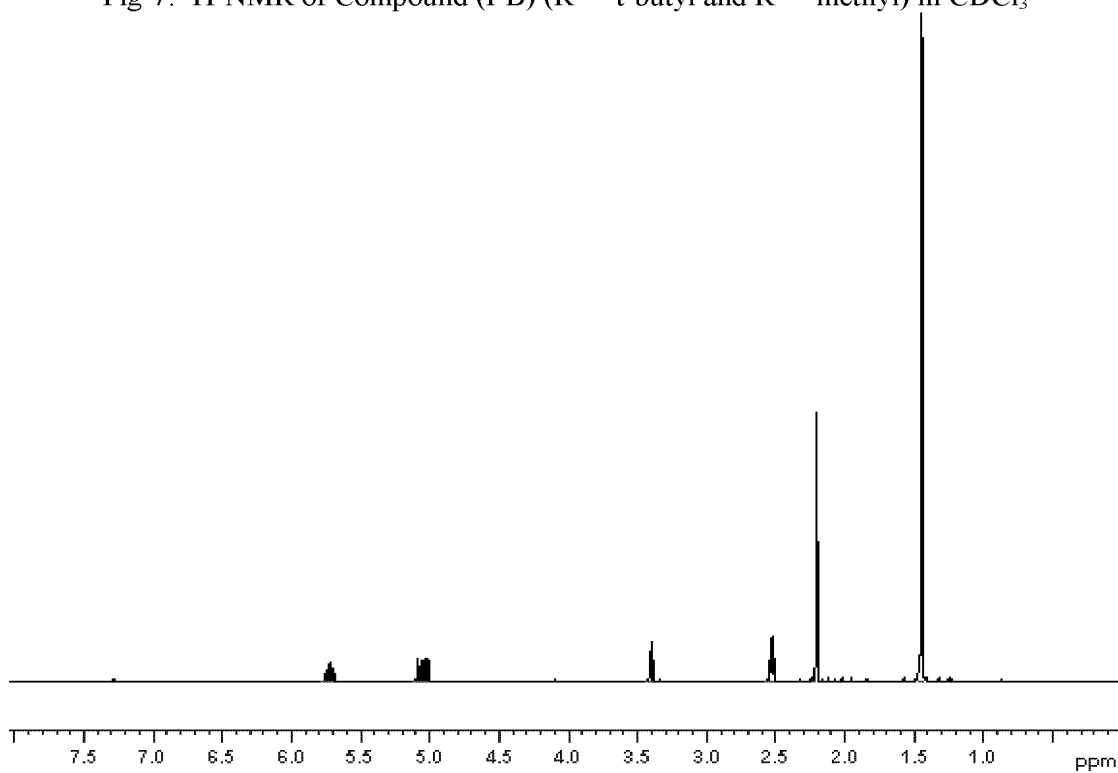
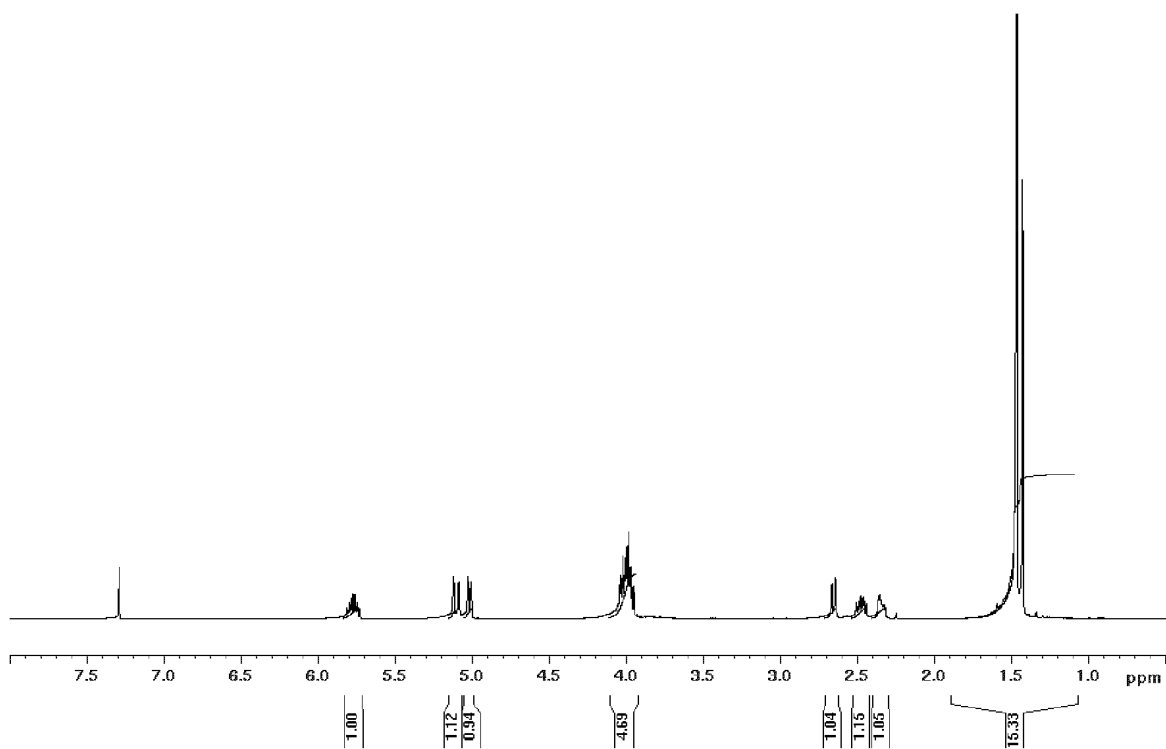
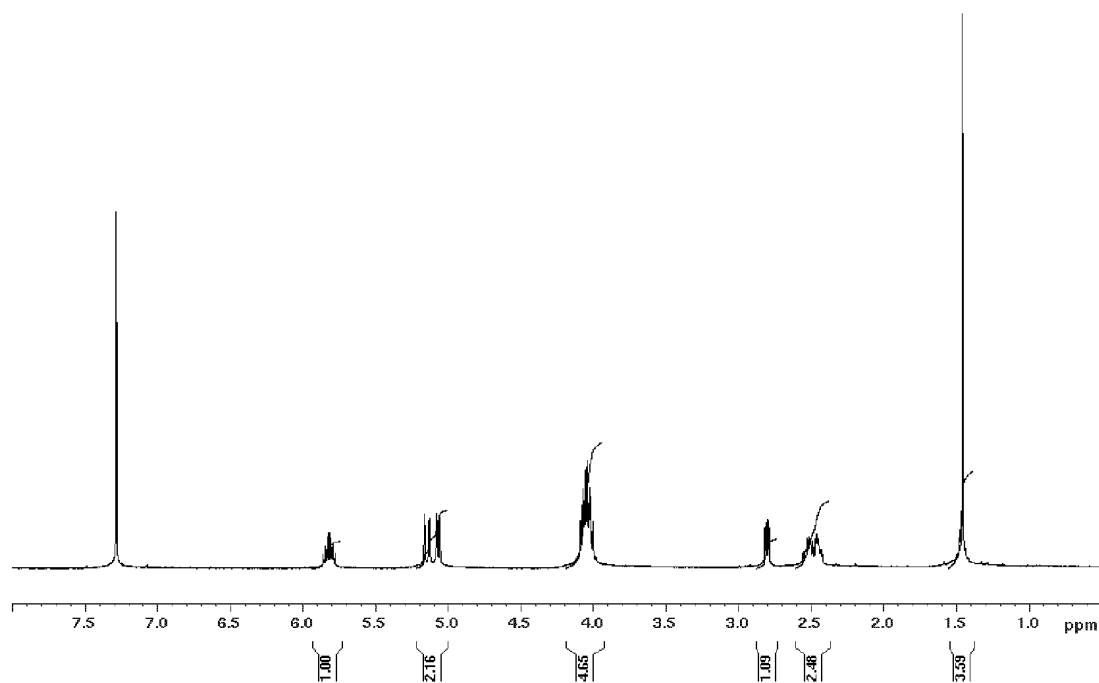
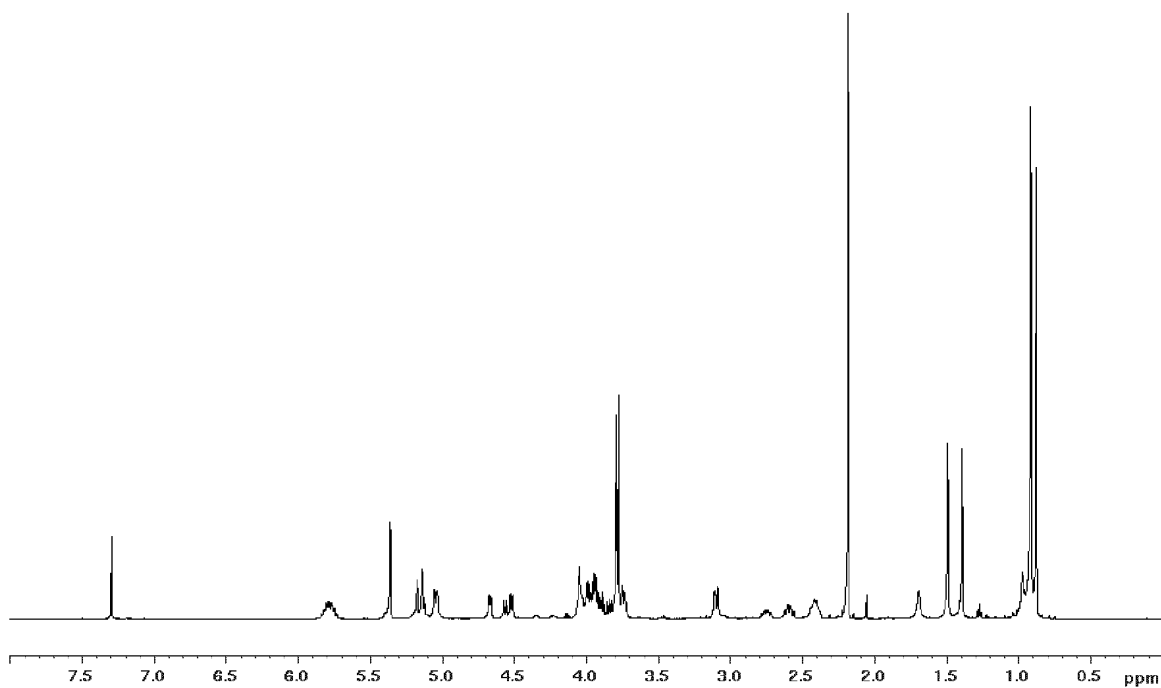
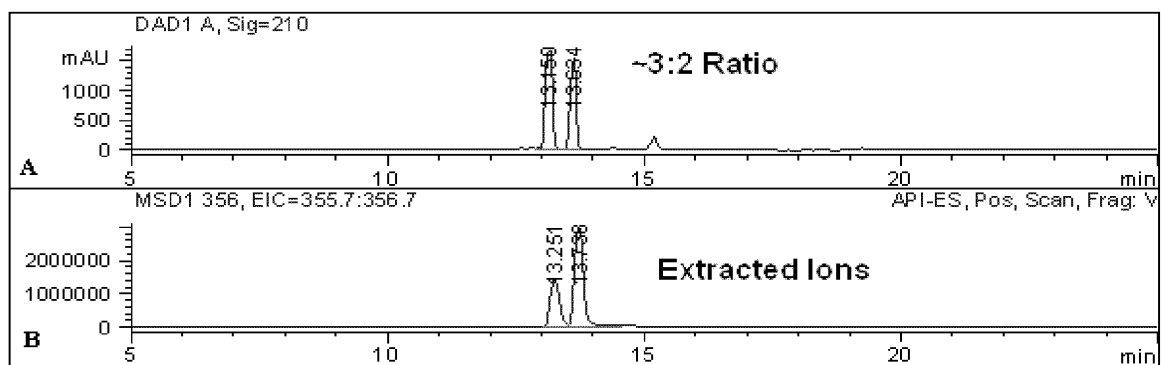


Fig-8: ¹H-NMR of the ester precursor to the Compound (II) in CDCl₃

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Fig-9: ¹H-NMR of Compound the protected ester precursor of the Compound (II) in CDCl₃Fig-10: ¹H-NMR of Compound (II) in CDCl₃

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Fig-11a: ¹H-NMR of Compound (III-1B) (R¹ = t-butyl and R² = methyl) in CDCl₃Fig-11b: LC-MS of Compound (III-1B) (R¹ = t-butyl and R² = methyl)

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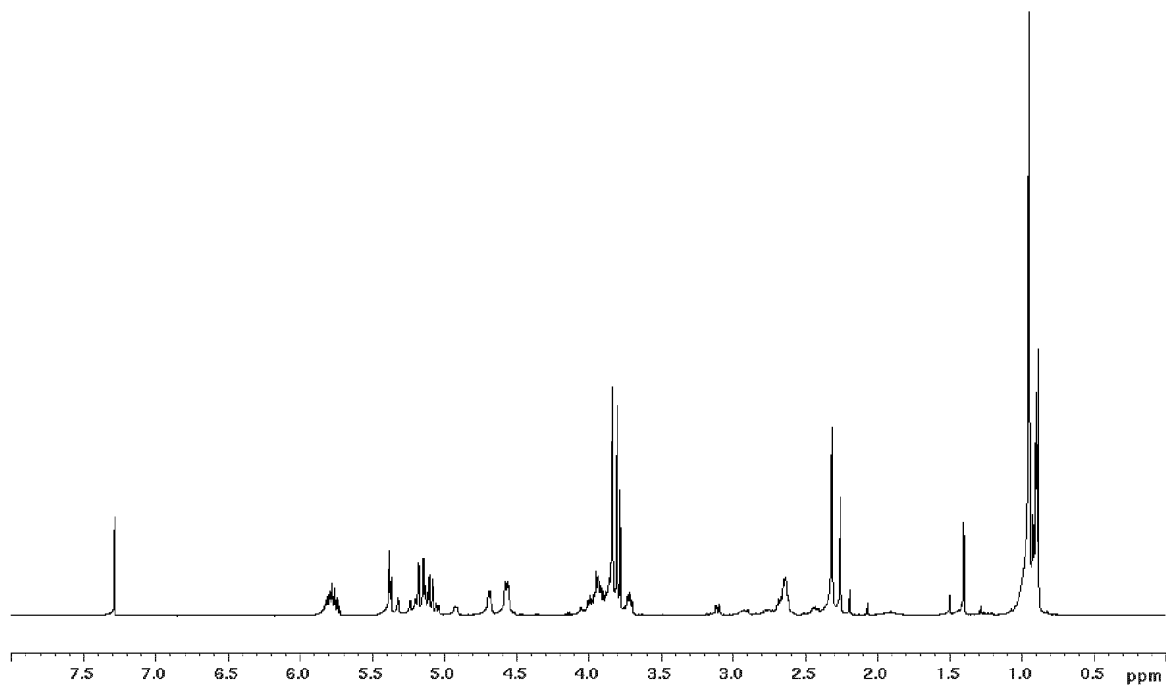


Fig-12a: ^1H -NMR of Compound (IV-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

14/47

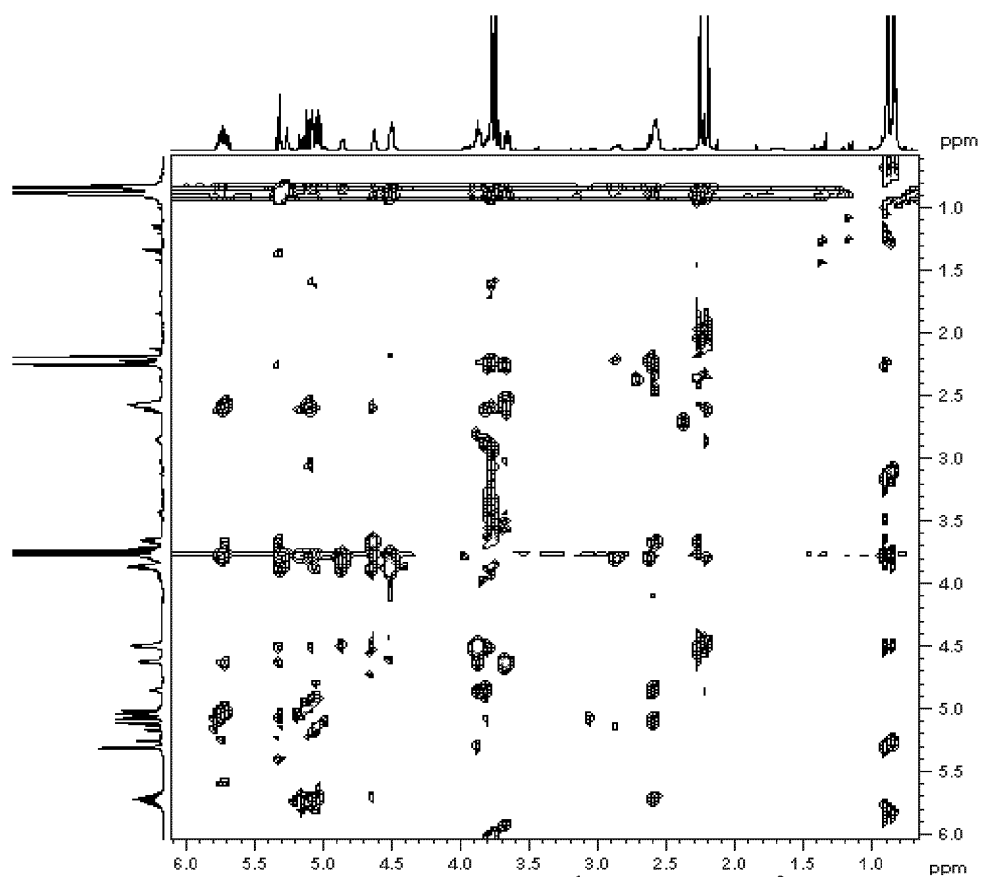
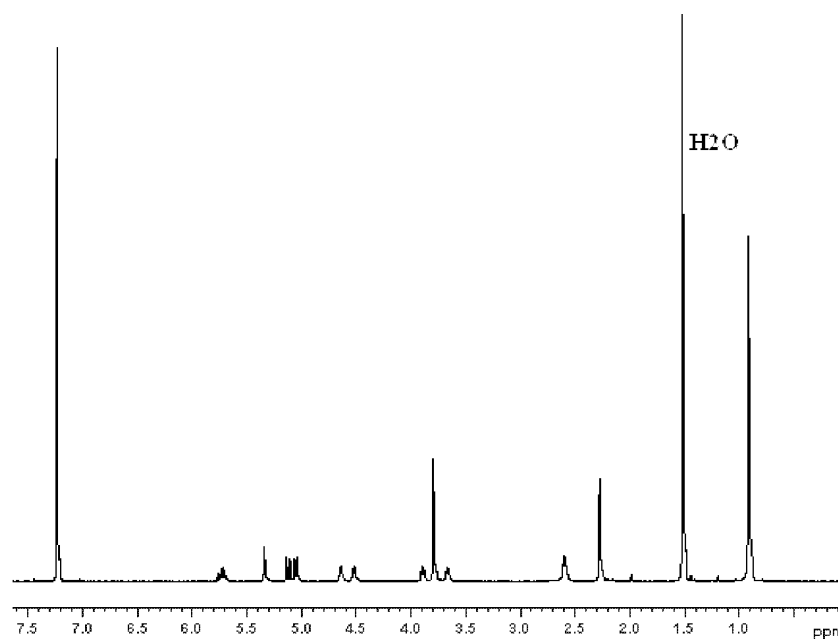
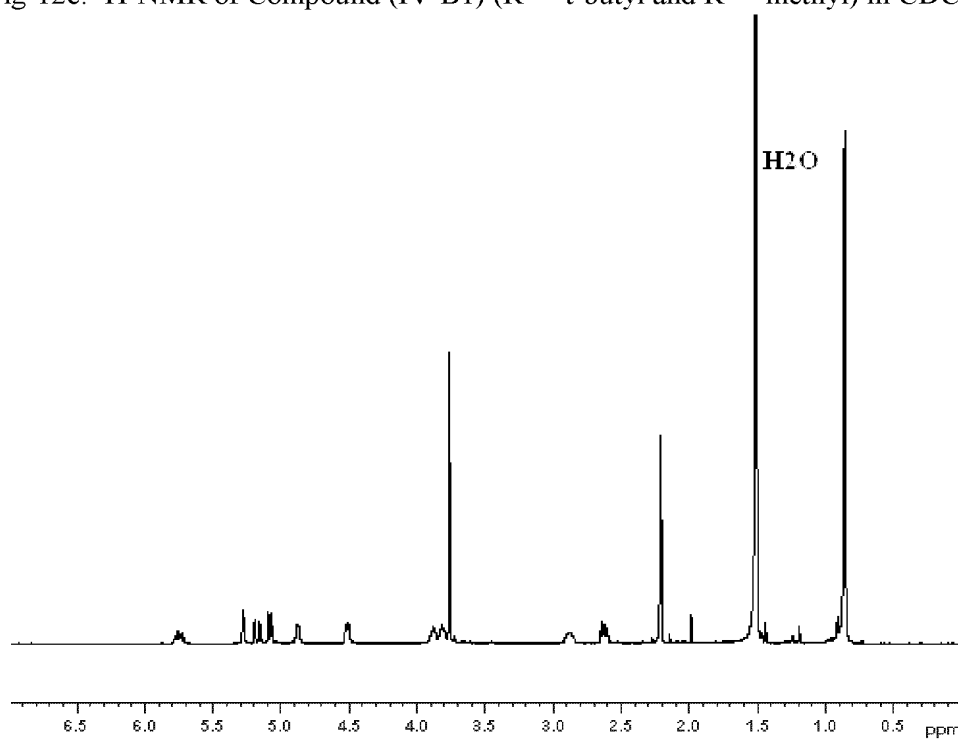
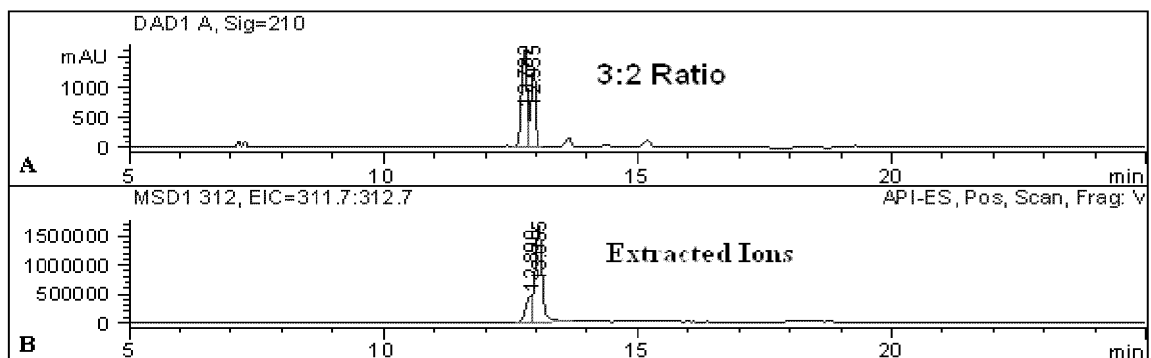
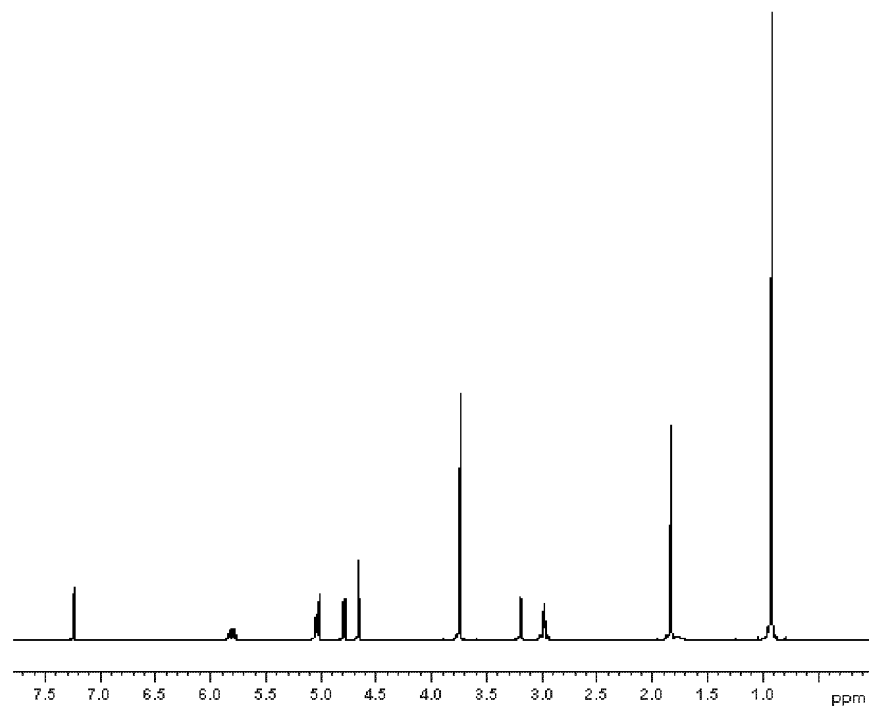


Fig-12b: NOESY of Compound (IV-B) (R^1 = t-butyl and R^2 = methyl)

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Fig-12c: ¹H-NMR of Compound (IV-B1) (R¹ = t-butyl and R² = methyl) in CDCl₃.Fig-12d: ¹H-NMR of Compound (IV-B2) (R¹ = t-butyl and R² = methyl) in CDCl₃.

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Fig-12e: LC-MS of Compound (IV-B) ($R^1 = t\text{-butyl}$ and $R^2 = \text{methyl}$)Fig-13: ^1H NMR of Compound (VI-B) in CDCl_3 ($R^1 = t\text{-butyl}$ and $R^2 = \text{methyl}$)

17/47

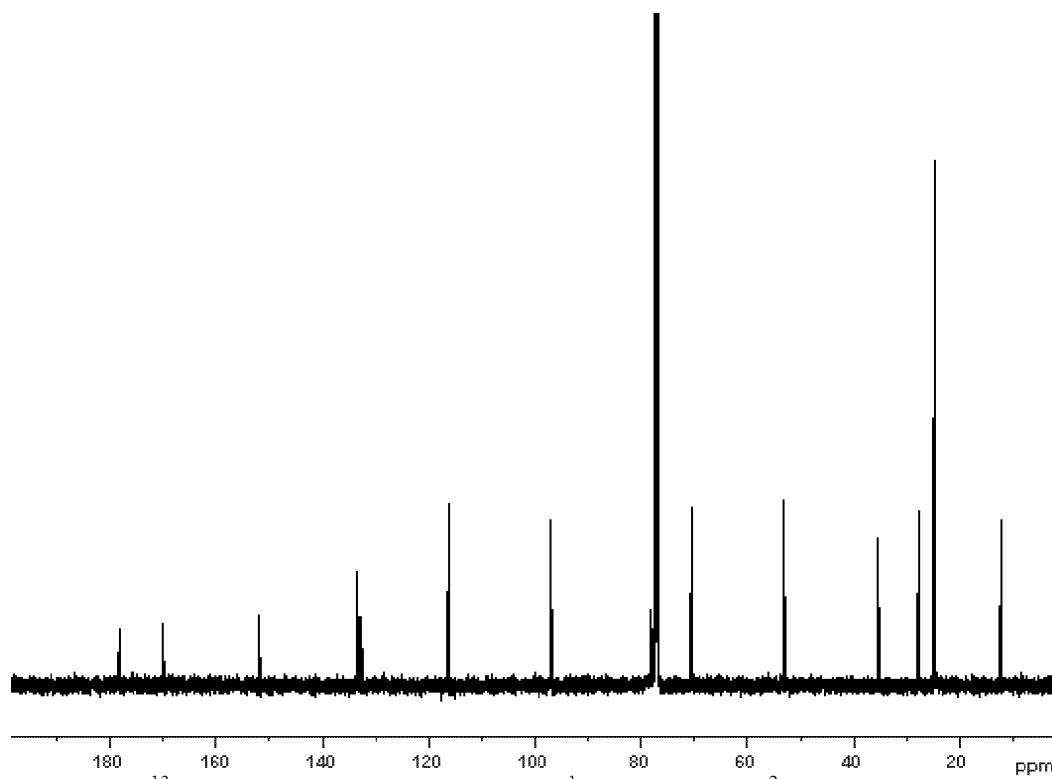


Fig-14: ^{13}C NMR of Compound (VI-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

18/47

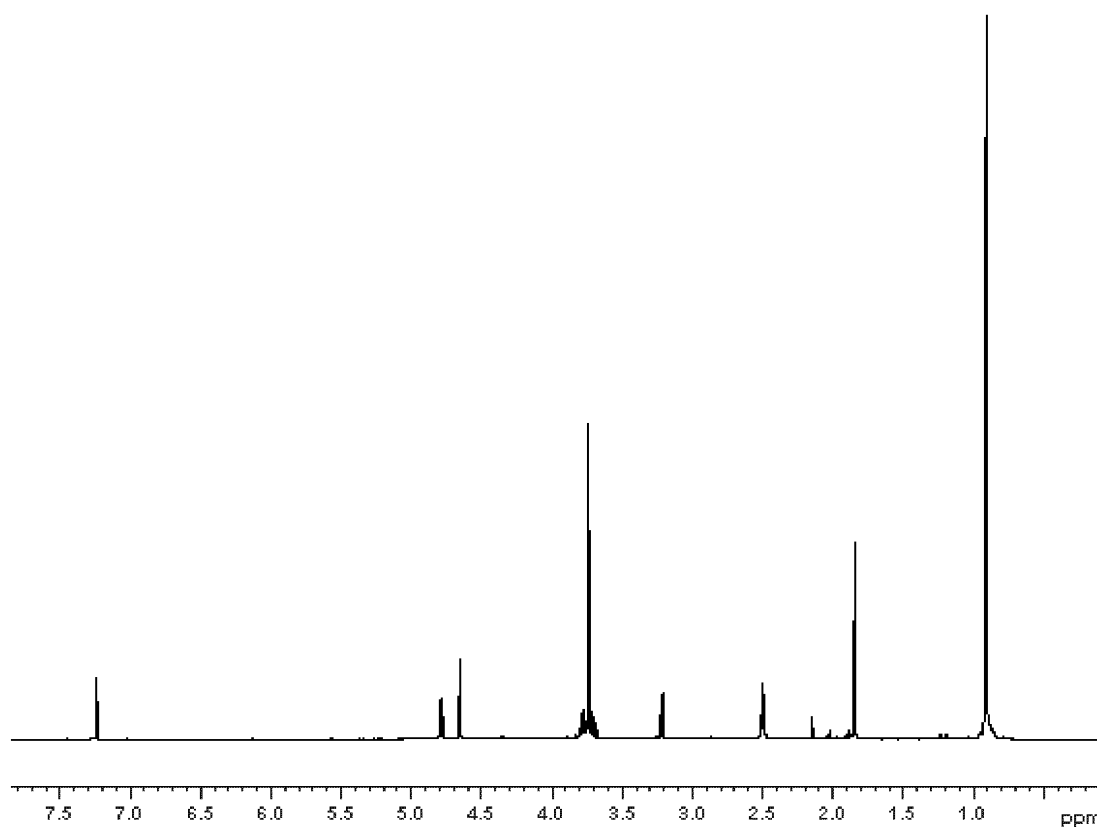


Fig. 15: ^1H NMR spectrum of Compound (VII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

19/47

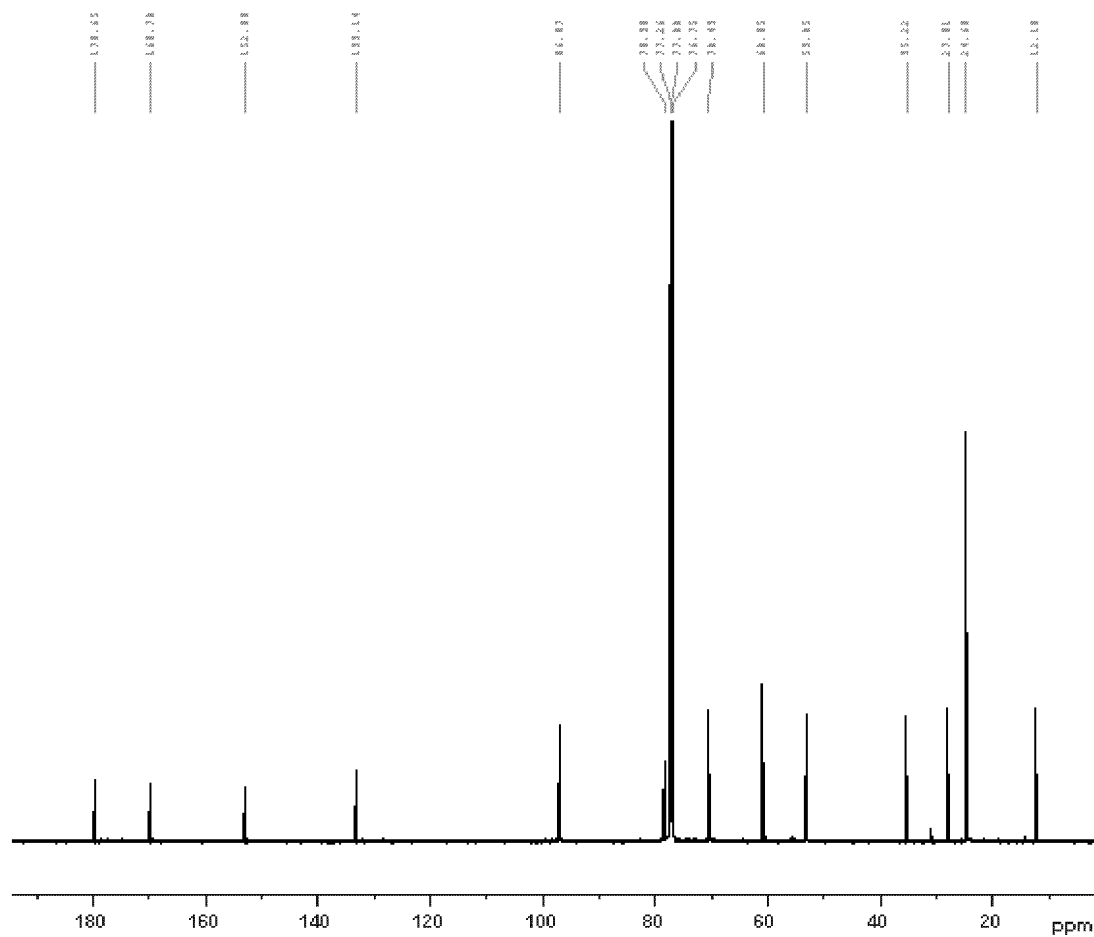


Fig. 16: ^{13}C NMR spectrum of Compound (VII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

20/47

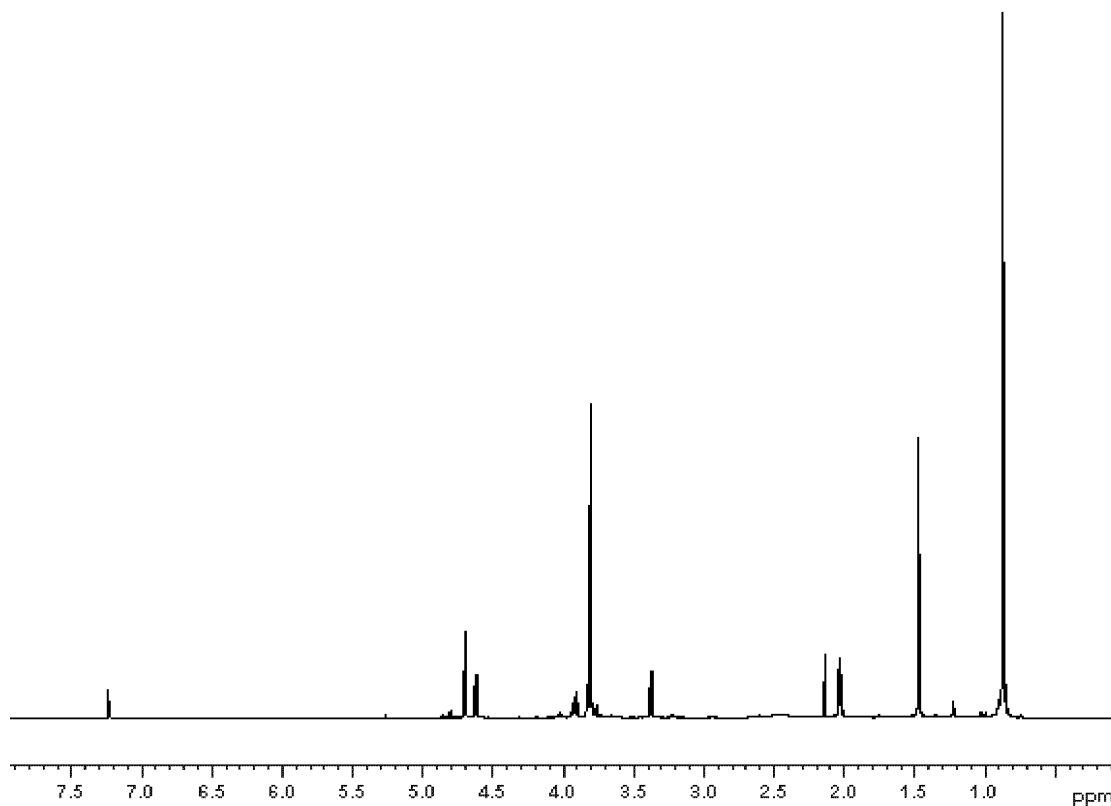


Fig. 17: ¹H NMR spectrum of Compound (VIII-B) (R¹ = t-butyl and R² = methyl) in CDCl₃

21/47

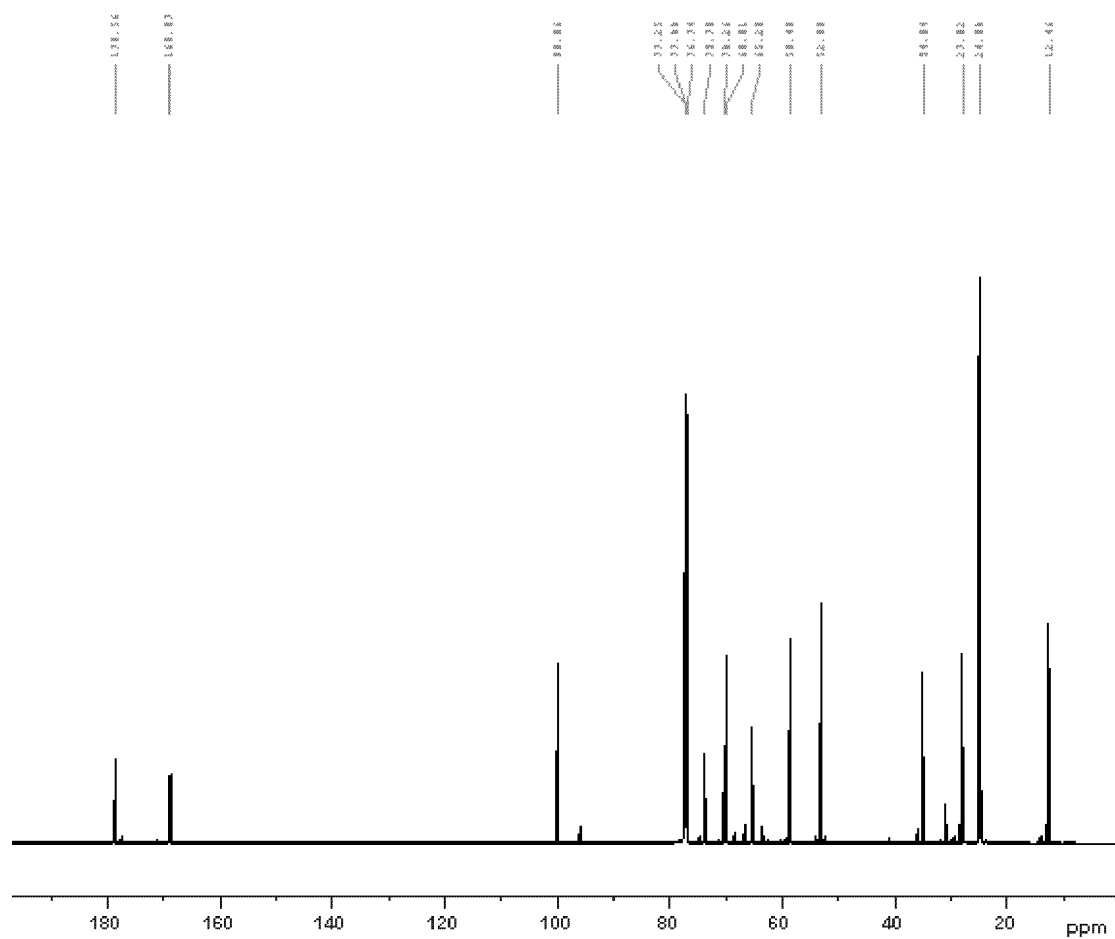


Fig. 18: ^{13}C NMR spectrum of Compound (VIII-B) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

22/47

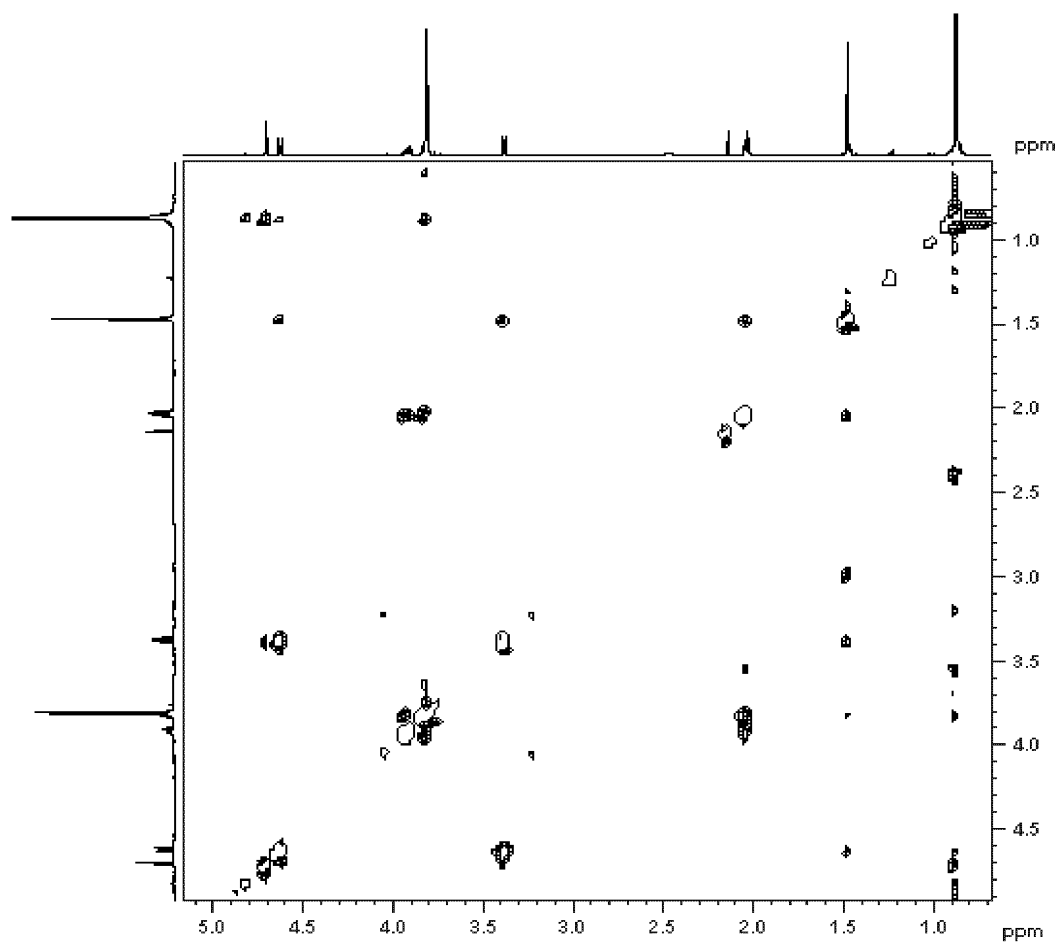


Fig. 19: NOESY spectrum of Compound (VIII-B) (R^1 = t-butyl and R^2 = methyl) in CDCl₃

23/47

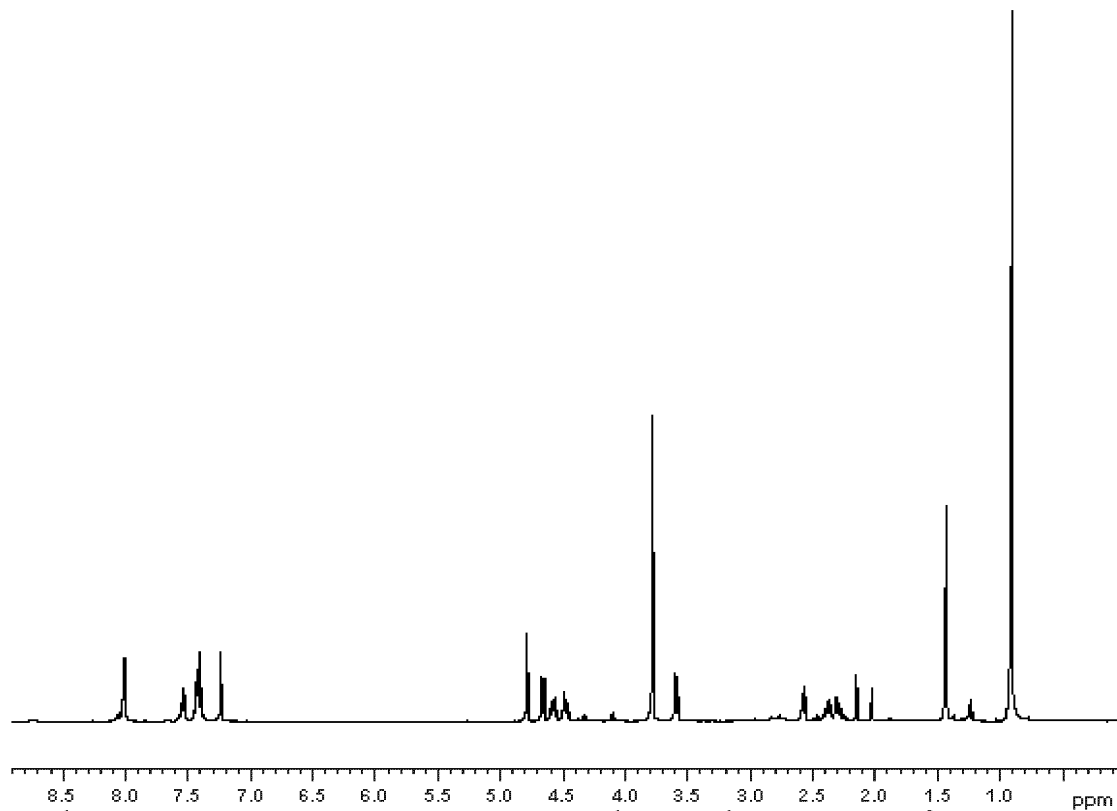


Fig. 20: ^1H NMR spectrum of Compound (X-1B) ($\text{PG}^1 = \text{Bz}$, $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

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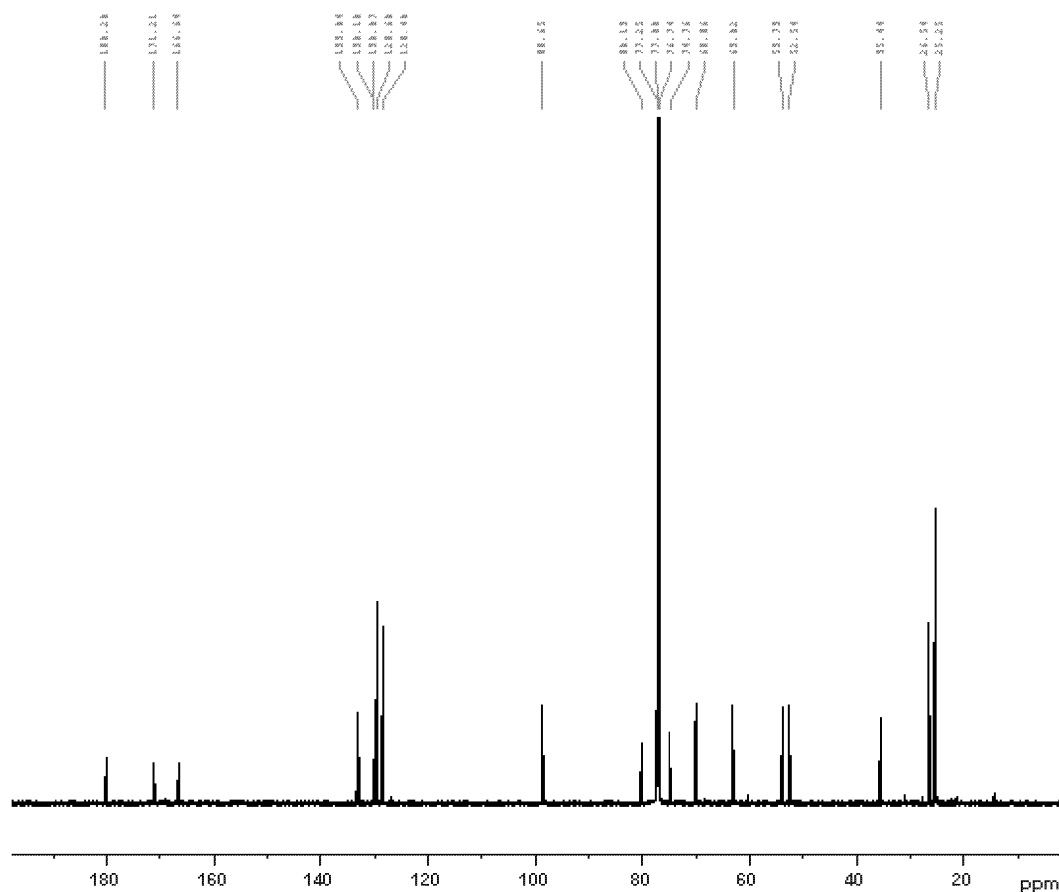


Fig. 21: ^{13}C NMR spectrum of Compound (X-1B) ($\text{PG}^1 = \text{Bz}$, $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

25/47

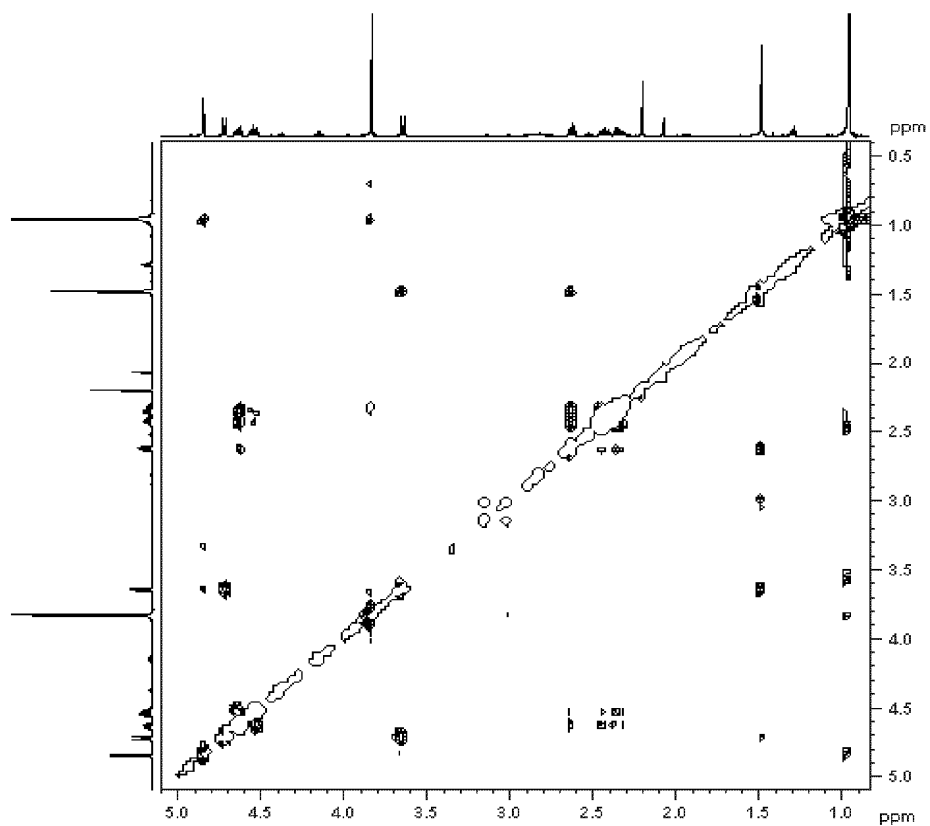


Fig. 22: NOESY spectrum of Compound (X-1B) ($\text{PG}^1 = \text{Bz}$, $\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

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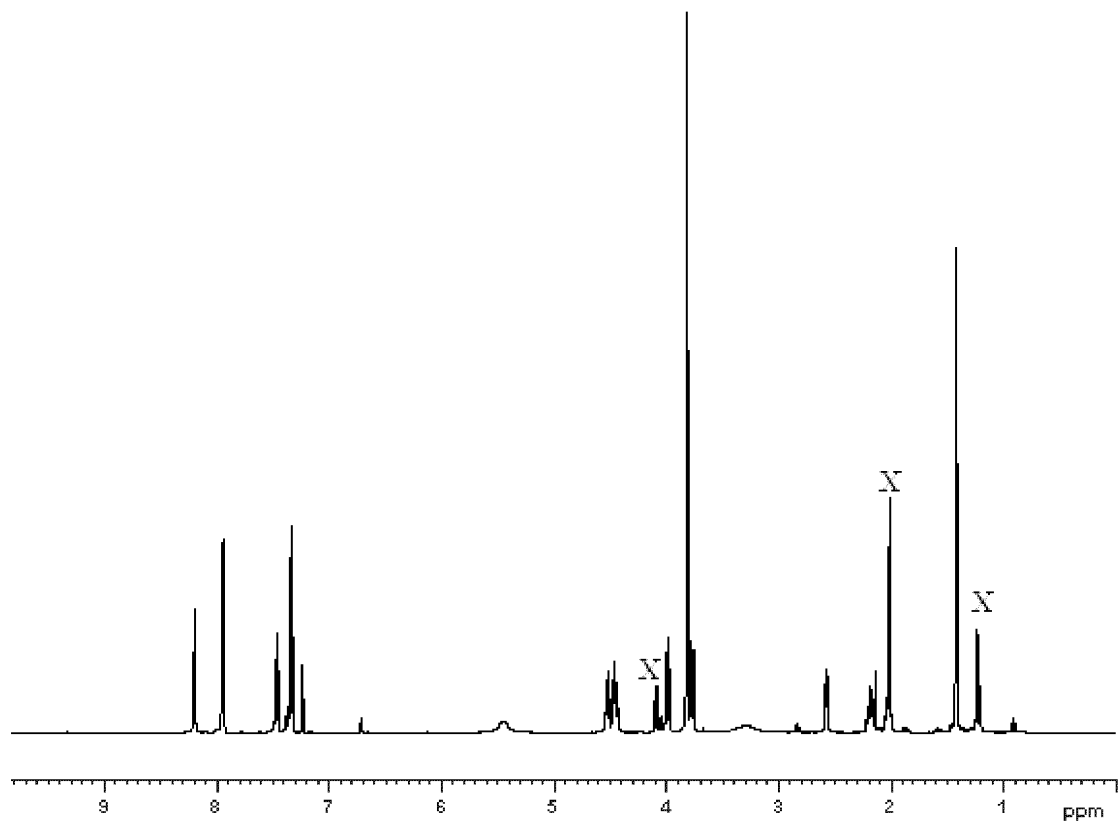


Fig. 23: ^1H NMR spectrum of Compound (XI-1B) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

27/47

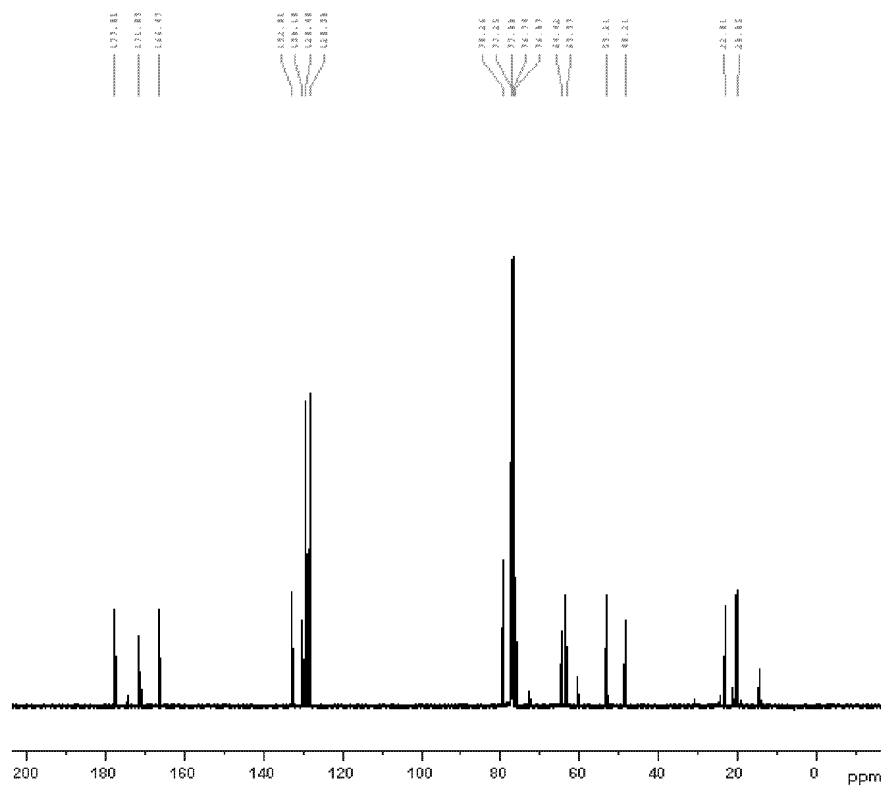


Fig. 24: ^{13}C NMR spectrum of Compound (XI-1B) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

28/47

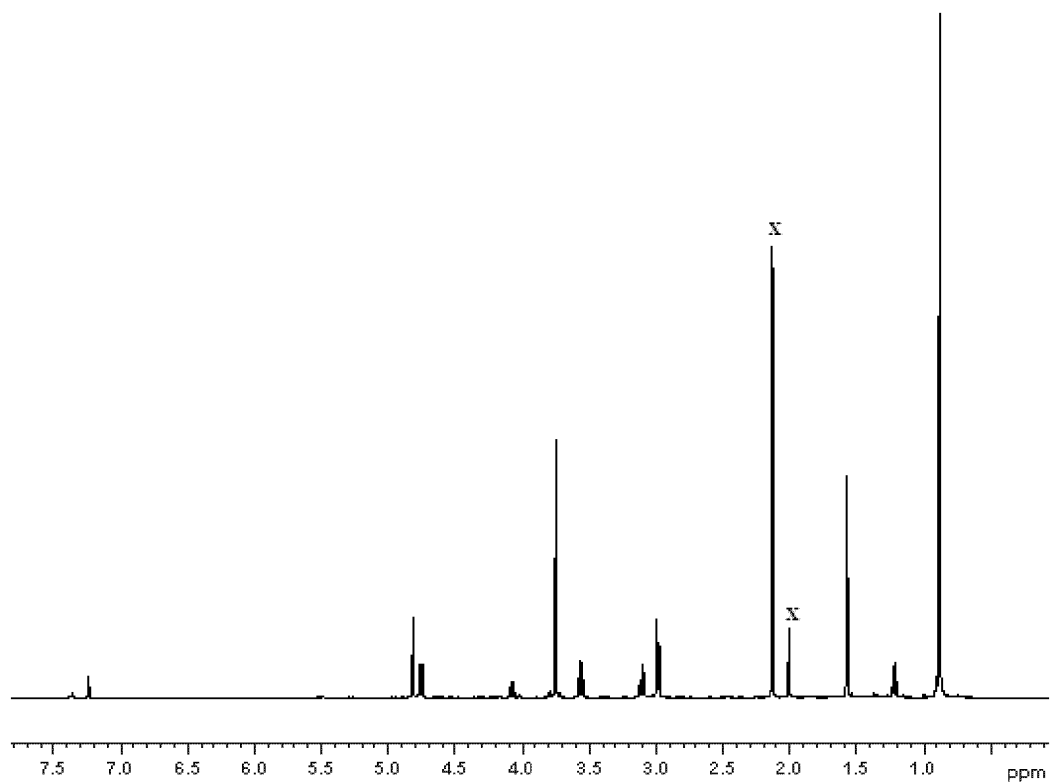


Fig. 25: ^1H NMR spectrum of Compound (X-2B) ($\text{R}^2 = \text{methyl}$) in CDCl_3

29/47

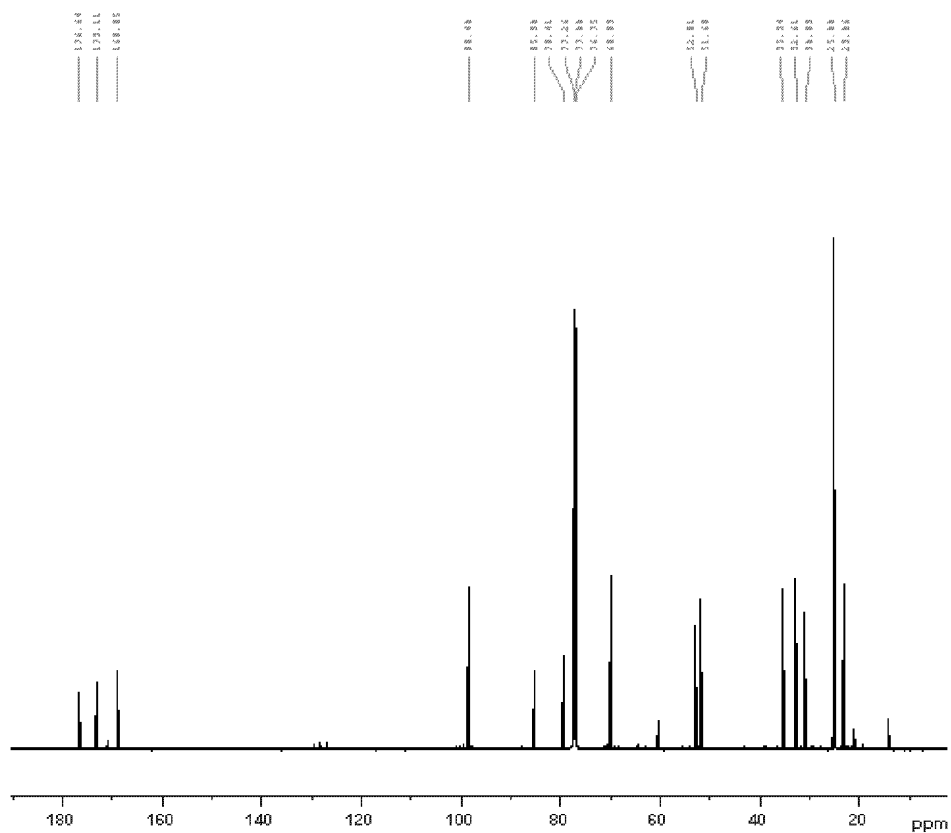


Fig. 26: ^{13}C NMR spectrum of Compound (X-2B) ($\text{R}^2 = \text{methyl}$) in CDCl_3

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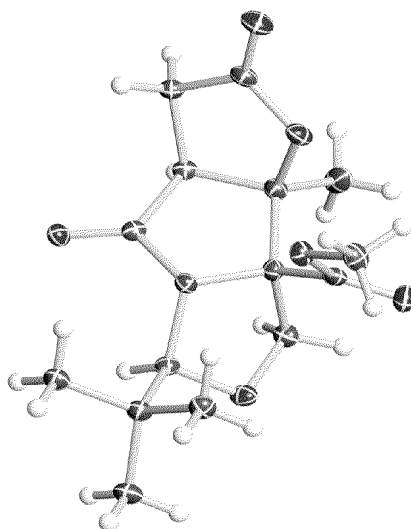


Fig. 27: X-ray crystal structure of Compound (X-2B) (R^2 = methyl)

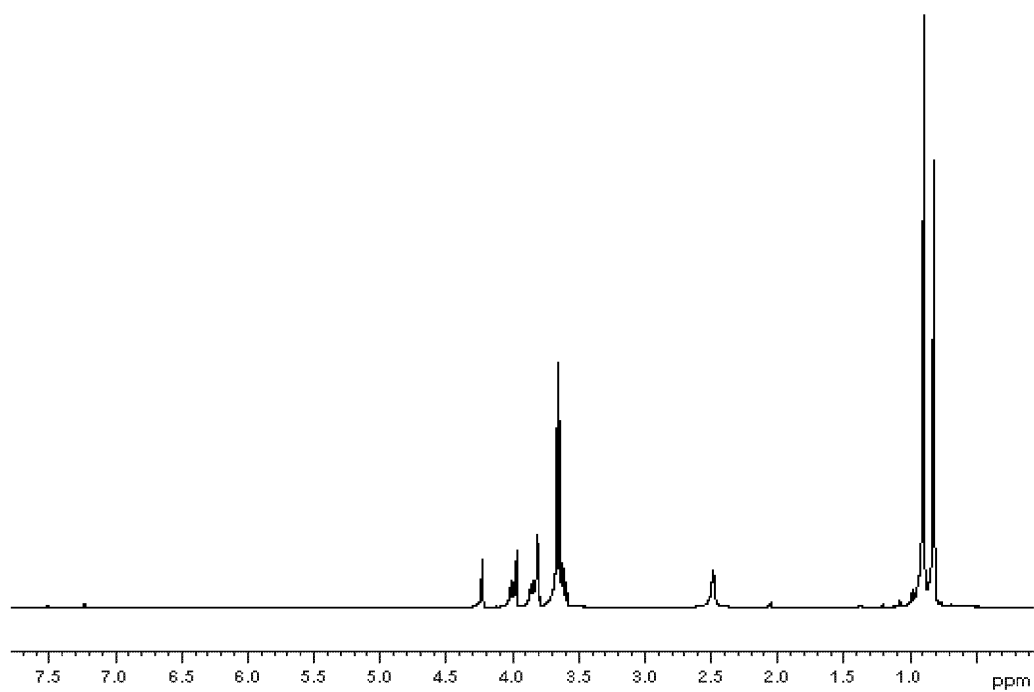


Fig-28: ¹H-NMR of Compound (I-A) (R^1 = t-butyl and R^2 = methyl) in CDCl₃

31/47

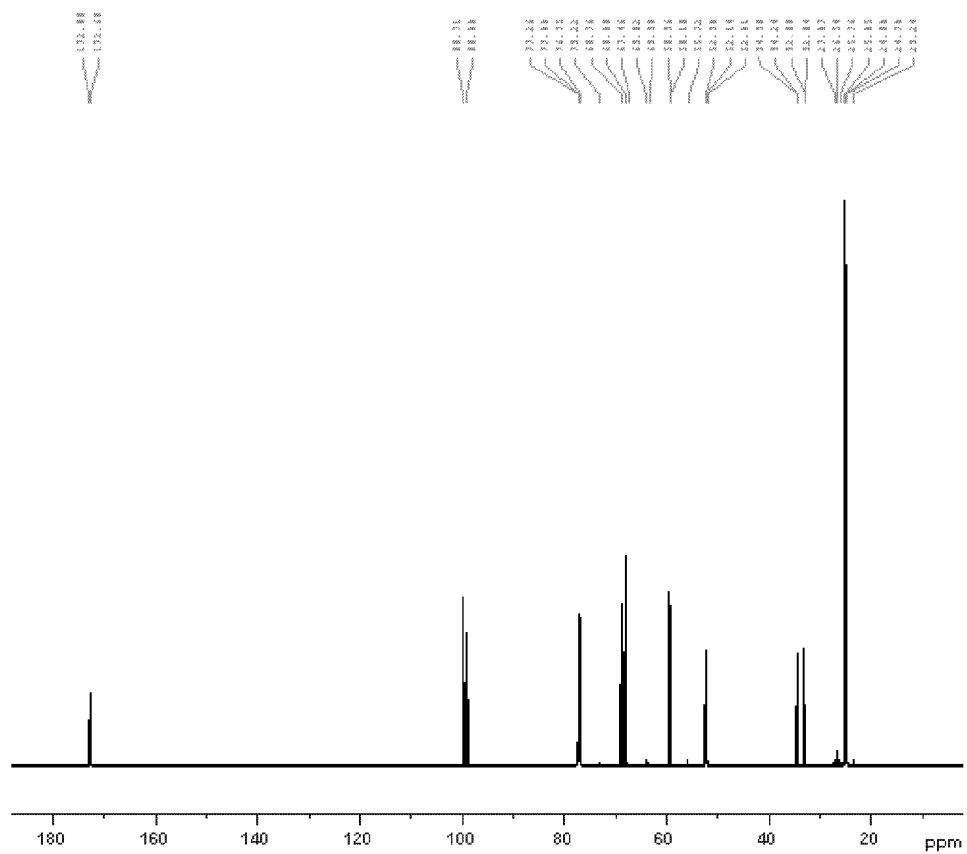


Fig-29: ^{13}C -NMR of Compound (I-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

32/47

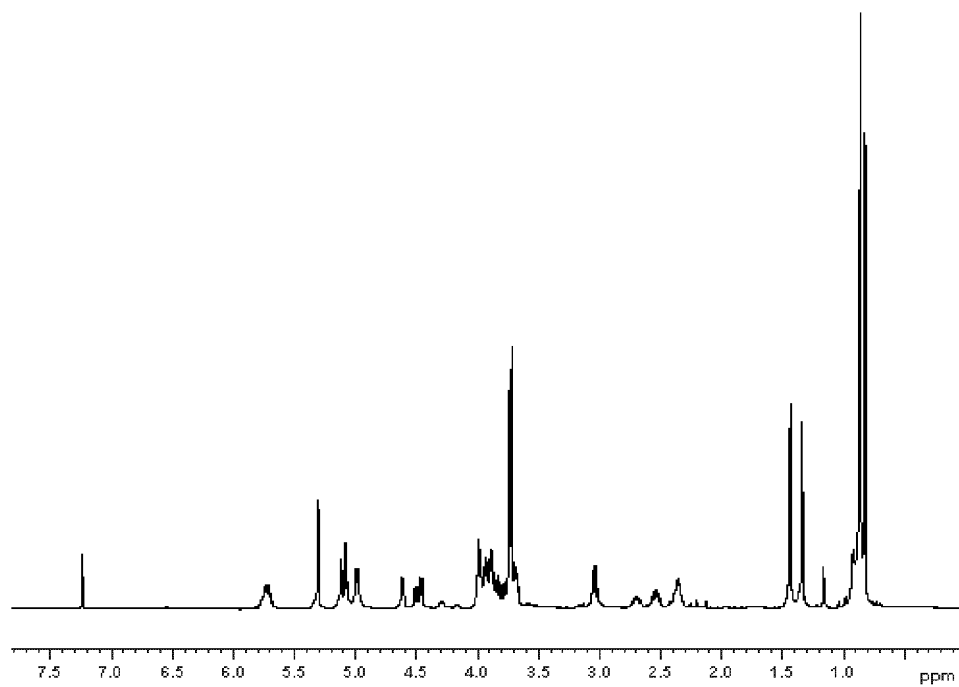


Fig. 30: ^1H NMR spectrum of Compound (III-1A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

33/47

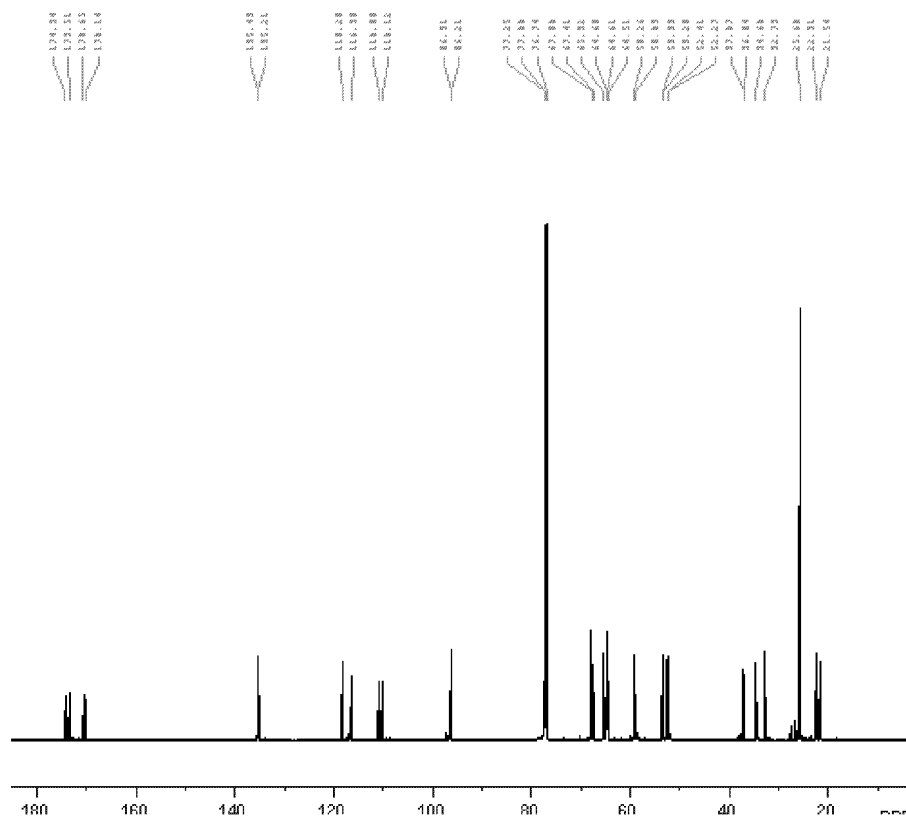


Fig. 31: ^{13}C NMR spectrum of Compound (III-1A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

34/47

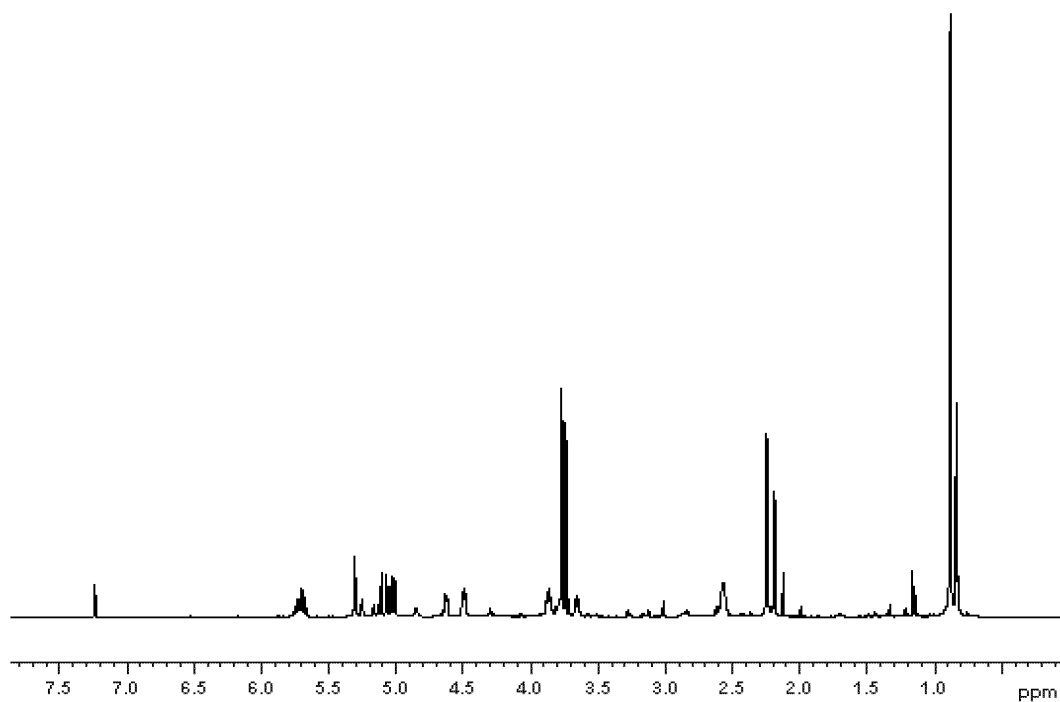
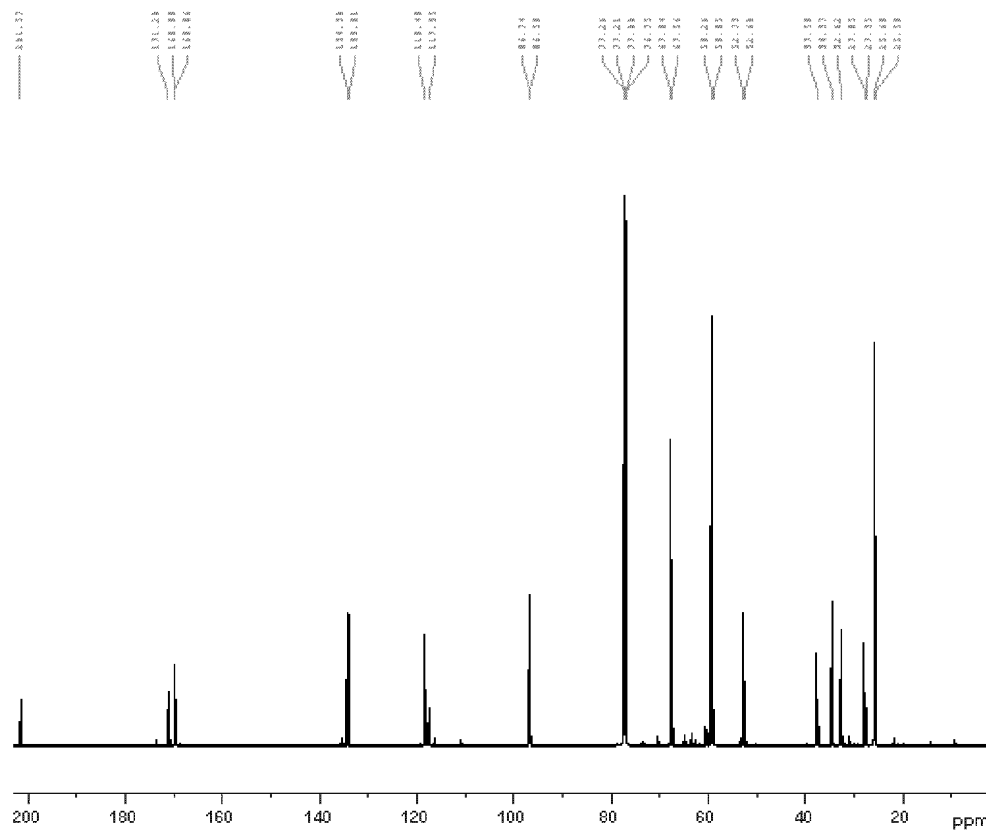


Fig. 32: ^1H NMR spectrum of Compound (IV-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

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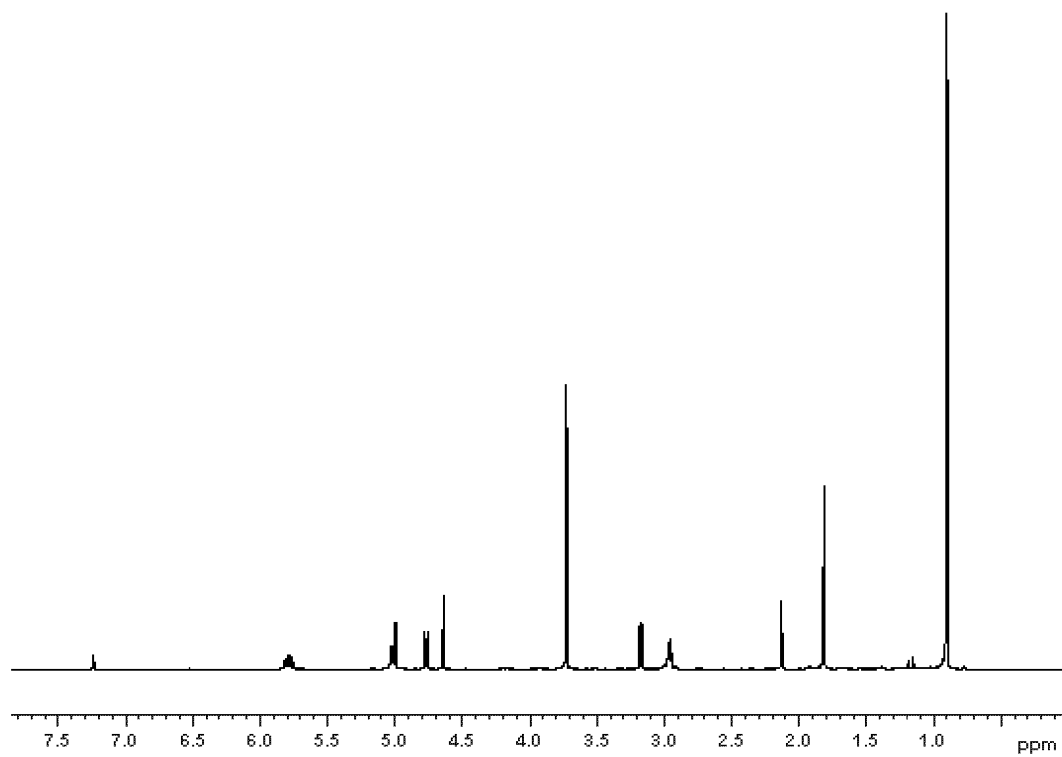


Fig. 34: ^1H NMR spectrum of Compound (VI-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

37/47

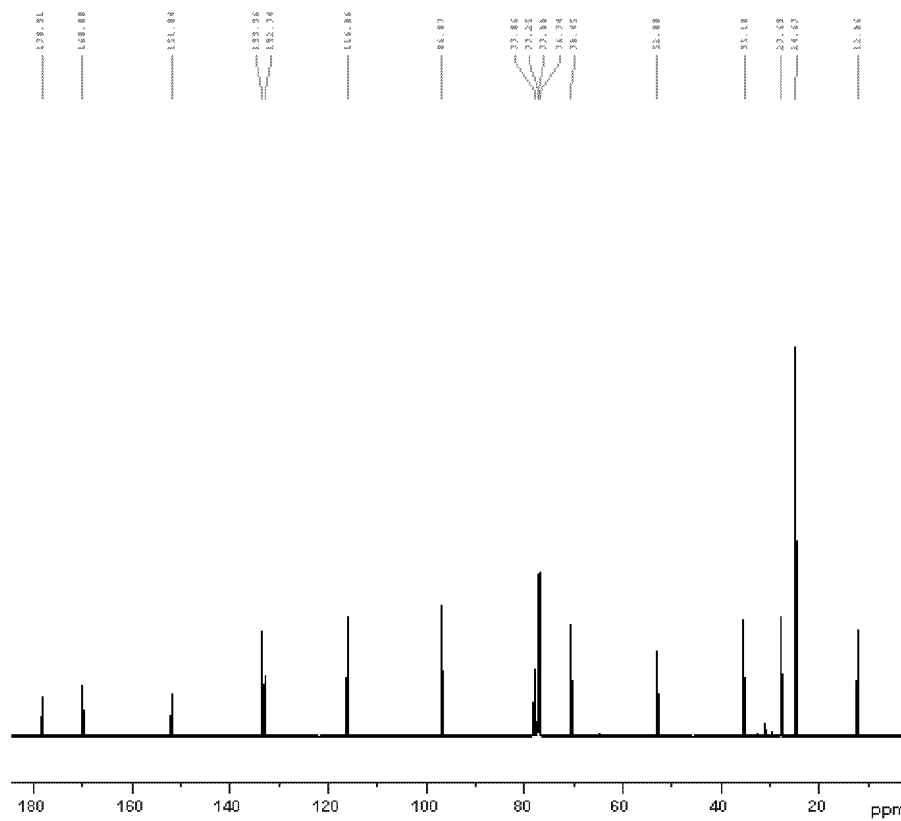


Fig. 35: ^{13}C NMR spectrum of Compound (VI-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

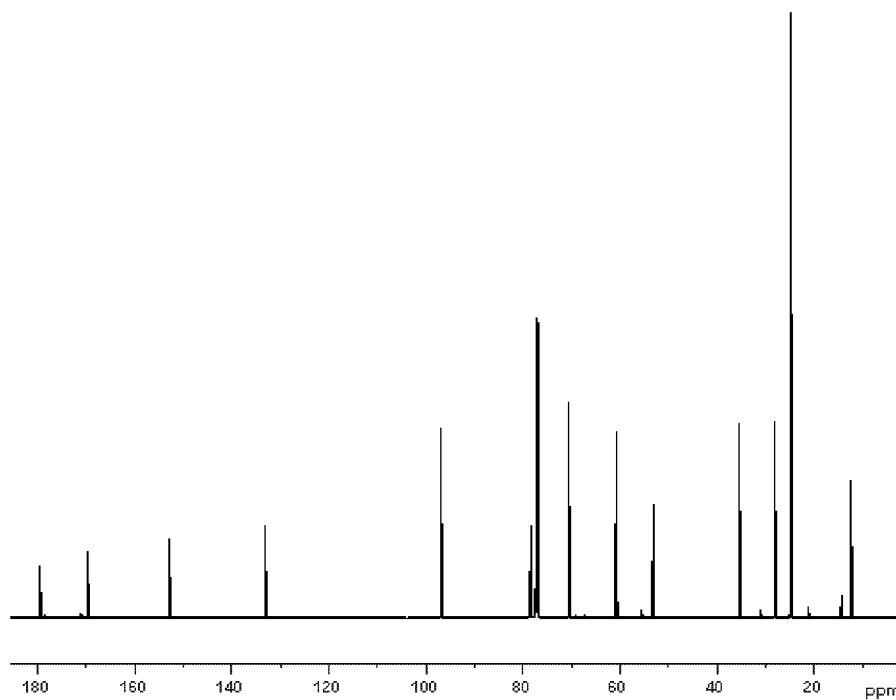
[illegible]

Fig. 37: ^{13}C NMR spectrum of Compound (VII-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

Chemical shifts (ppm) listed on the right:

- 178.58
- 172.88
- 168.88
- 88.81
- 77.25
- 77.00
- 76.74
- 72.82
- 71.28
- 68.28
- 65.35
- 58.58
- 52.88
- 34.89
- 34.89
- 26.89
- 22.89
- 24.89
- 24.89
- 12.49

Fig. 39: ^{13}C NMR spectrum of Compound (VIII-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

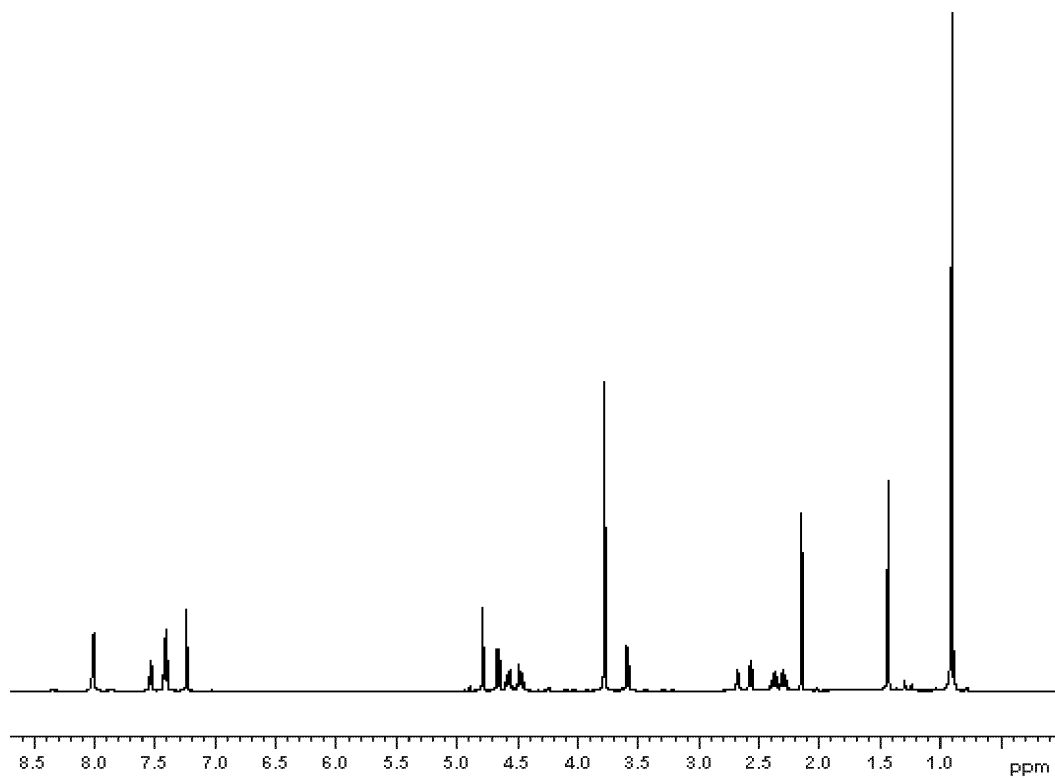


Fig. 40: ¹H NMR spectrum of Compound (X-1A) (PG¹ = Bz, R¹ = t-butyl and R² = methyl) in CDCl₃

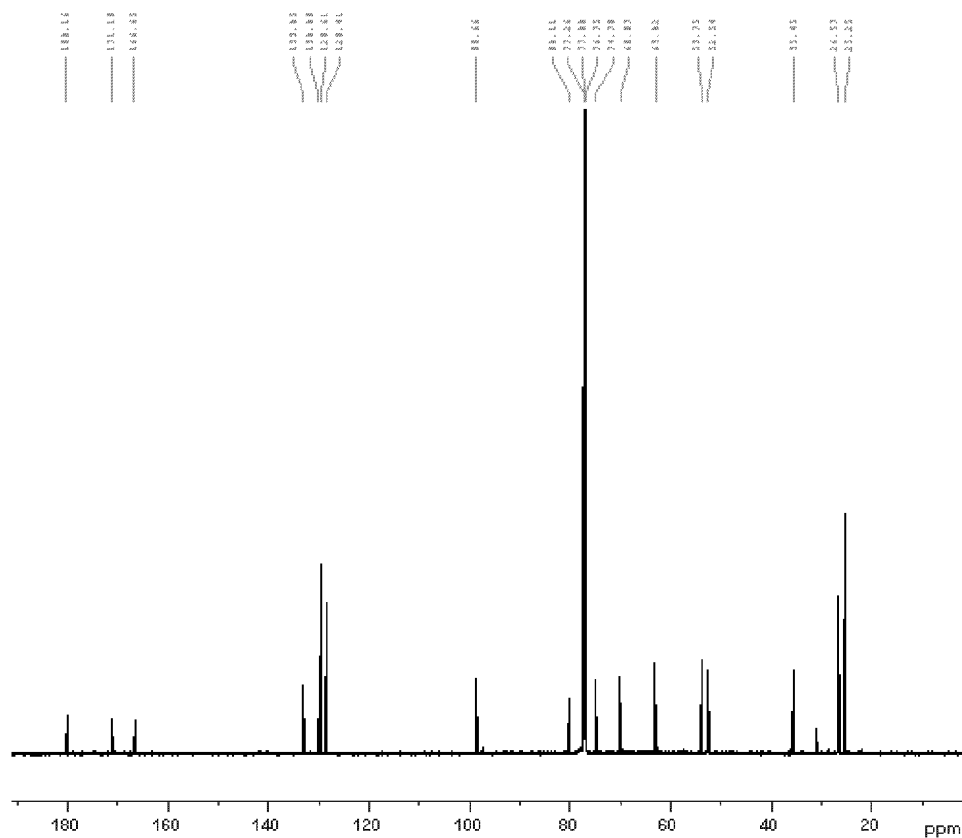


Fig. 41: ¹³C NMR spectrum of Compound (X-1A) (PG¹ = Bz, R¹ = t-butyl and R² = methyl) in CDCl₃

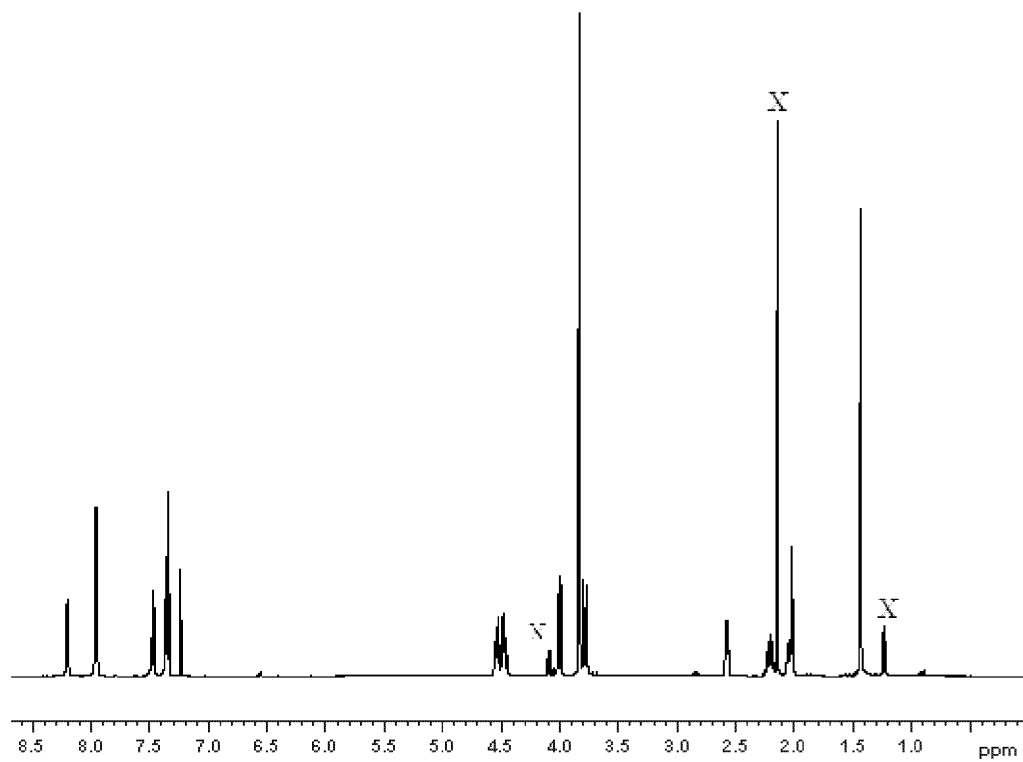


Fig. 42: ^1H NMR spectrum of Compound (XI-1A) ($\text{PG}^1 = \text{Bz}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

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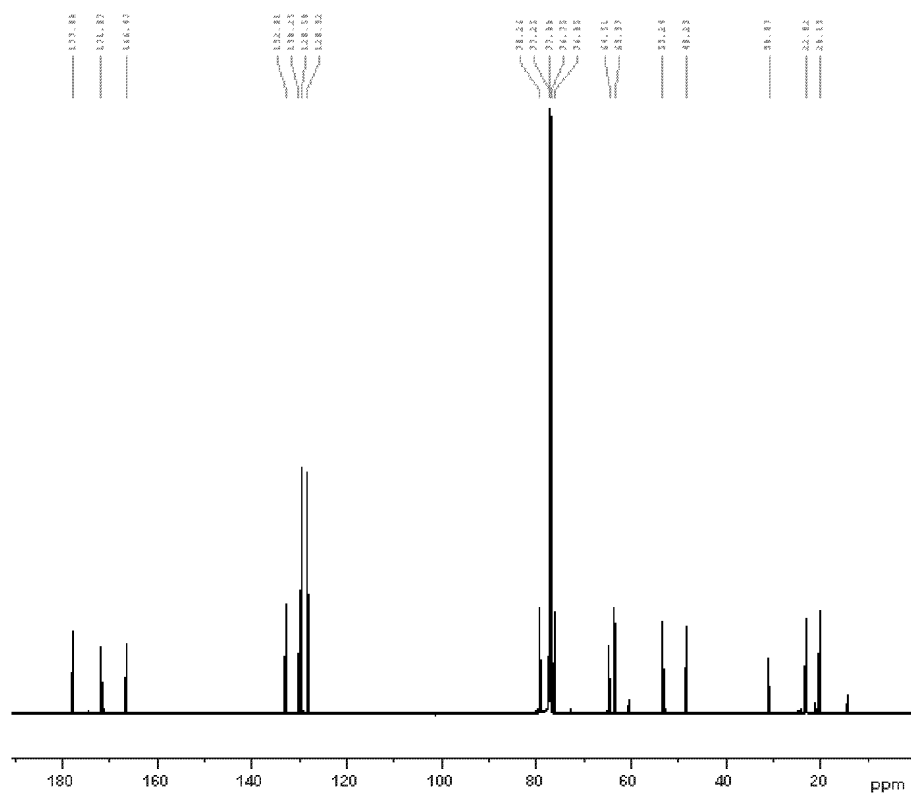


Fig. 43: ¹³C NMR spectrum of Compound (XI-1A) (PG¹ = Bz and R² = methyl) in CDCl₃

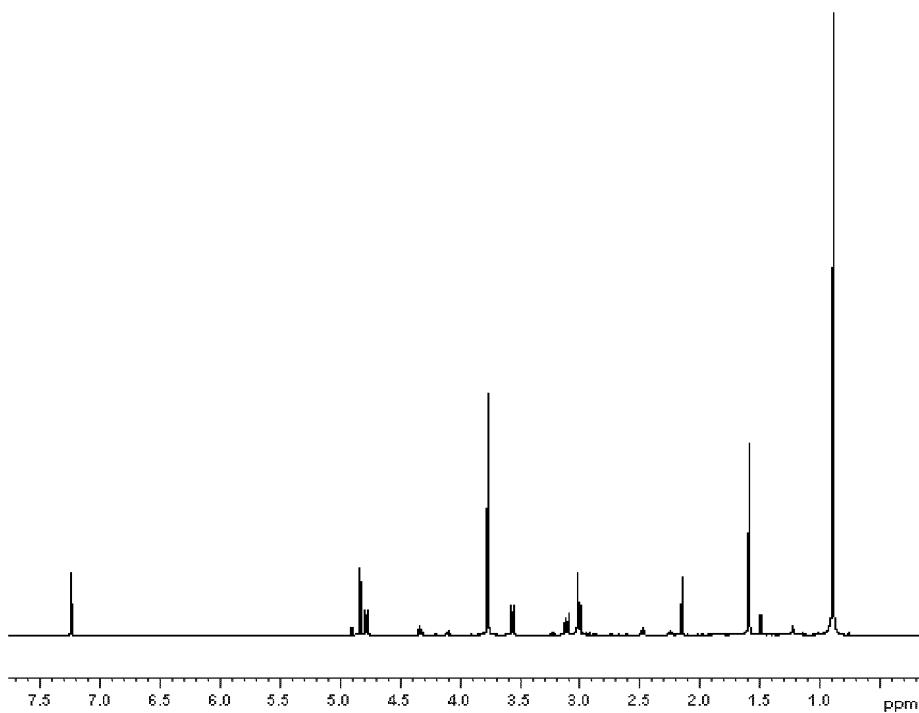


Fig. 44: ¹H NMR spectrum of Compound (X-2A) (R¹ = t-butyl and R² = methyl) in CDCl₃

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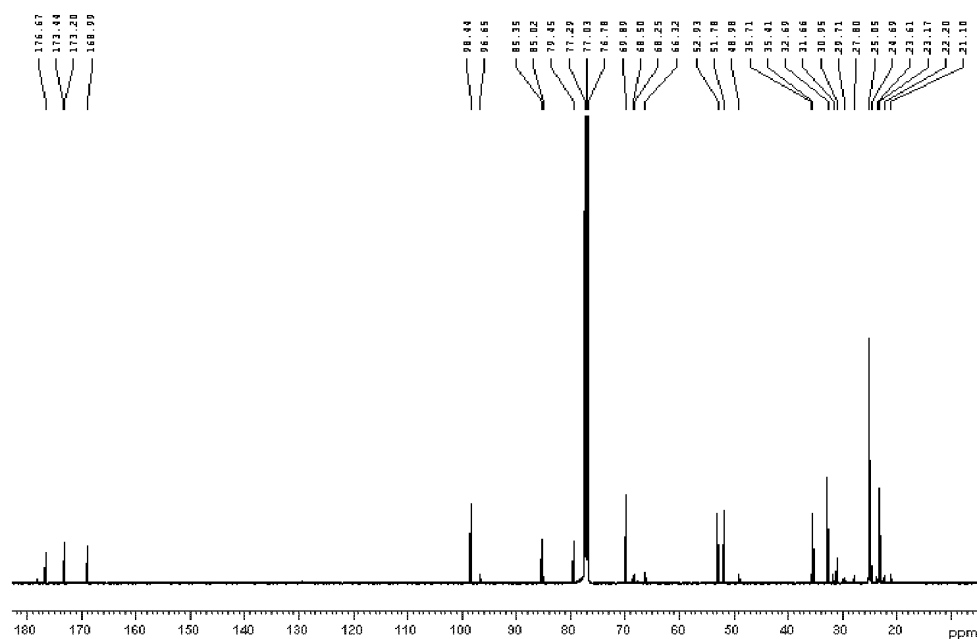


Fig. 45: ^{13}C NMR spectrum of Compound (X-2A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3

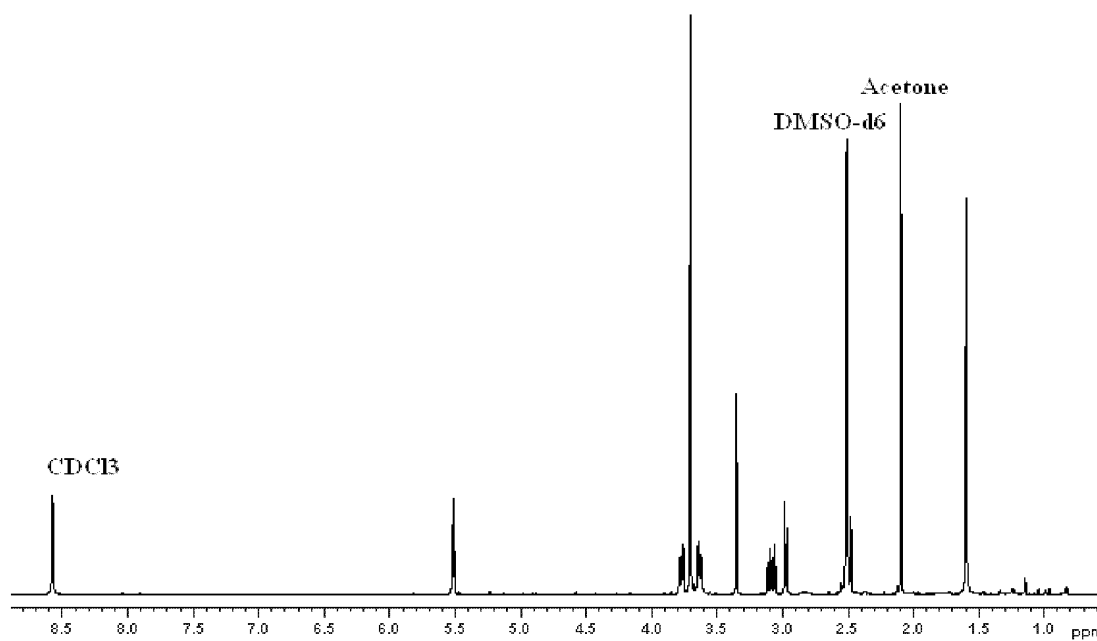


Fig. 46: ^1H NMR spectrum of Compound (XI-2A) ($\text{R}^2 = \text{methyl}$) in DMSO-d_6 and CDCl_3 mixture

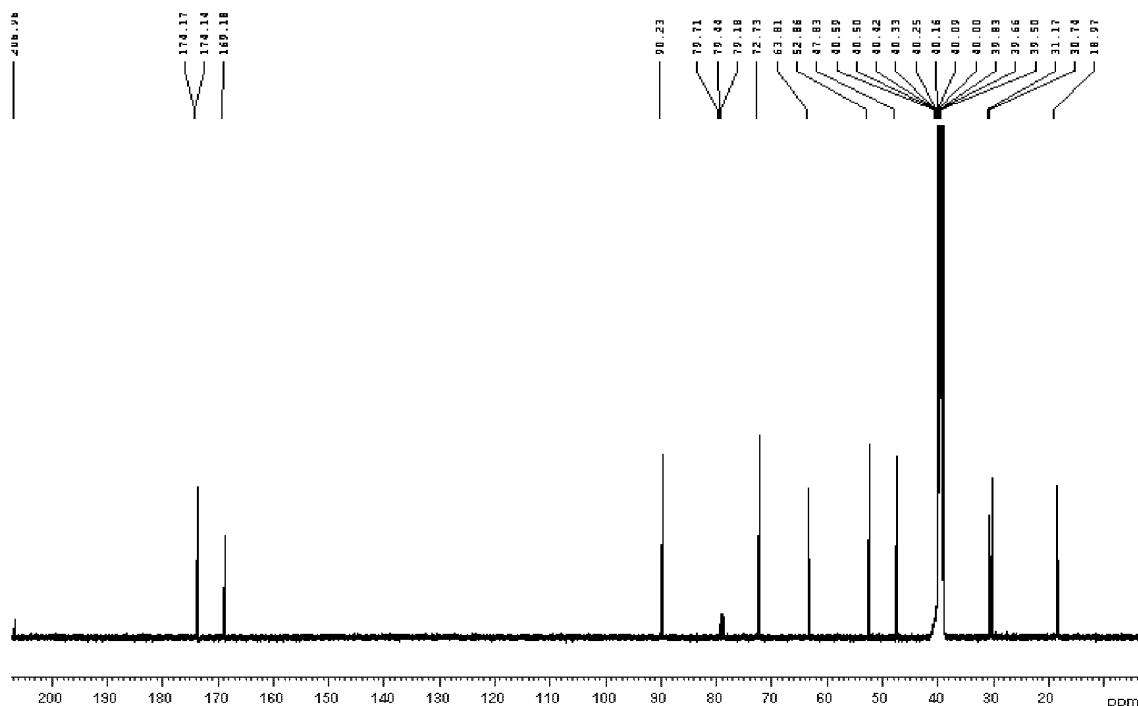


Fig. 47: ^{13}C NMR spectrum of Compound (XI-2A) ($\text{R}^2 = \text{methyl}$) in DMSO-d_6 and CDCl_3 mixture.

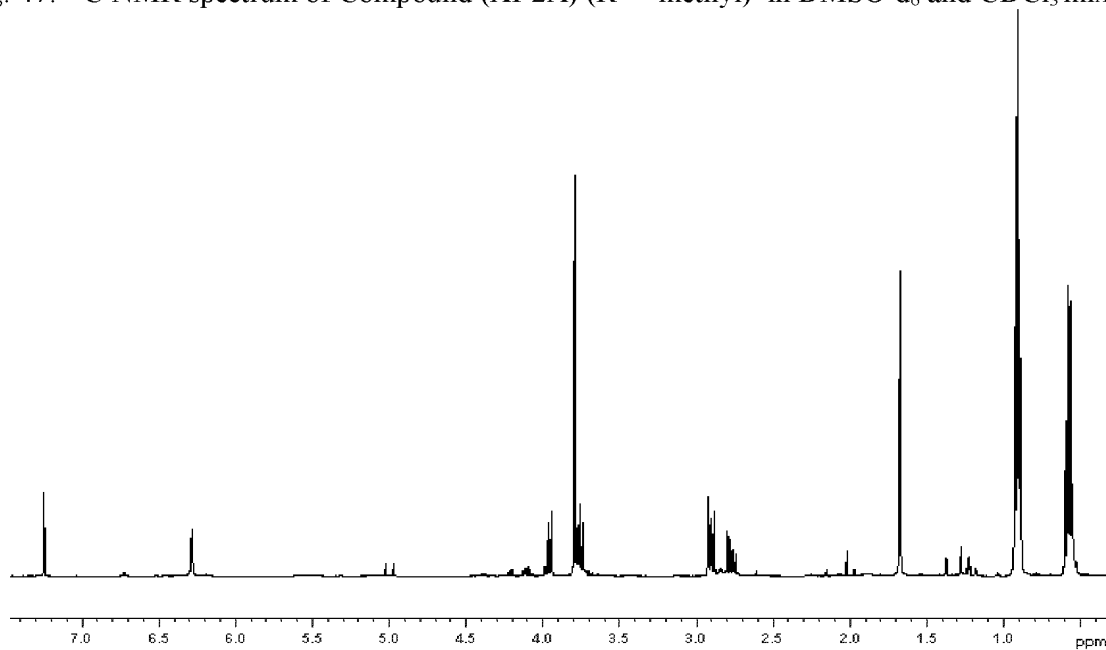
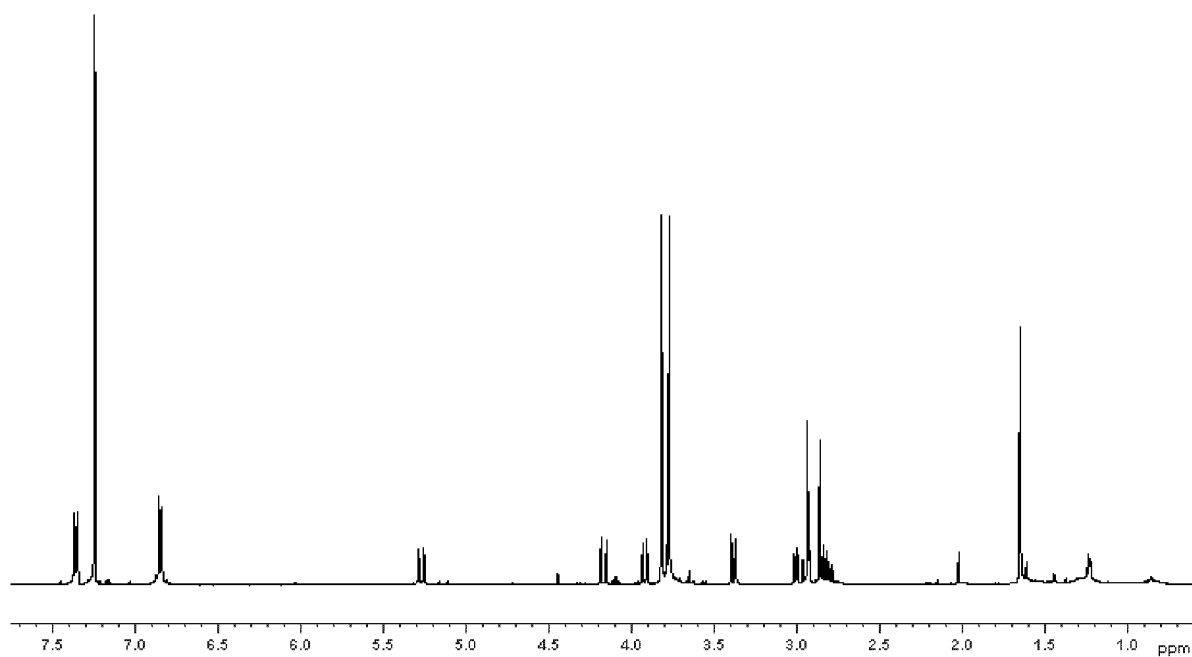
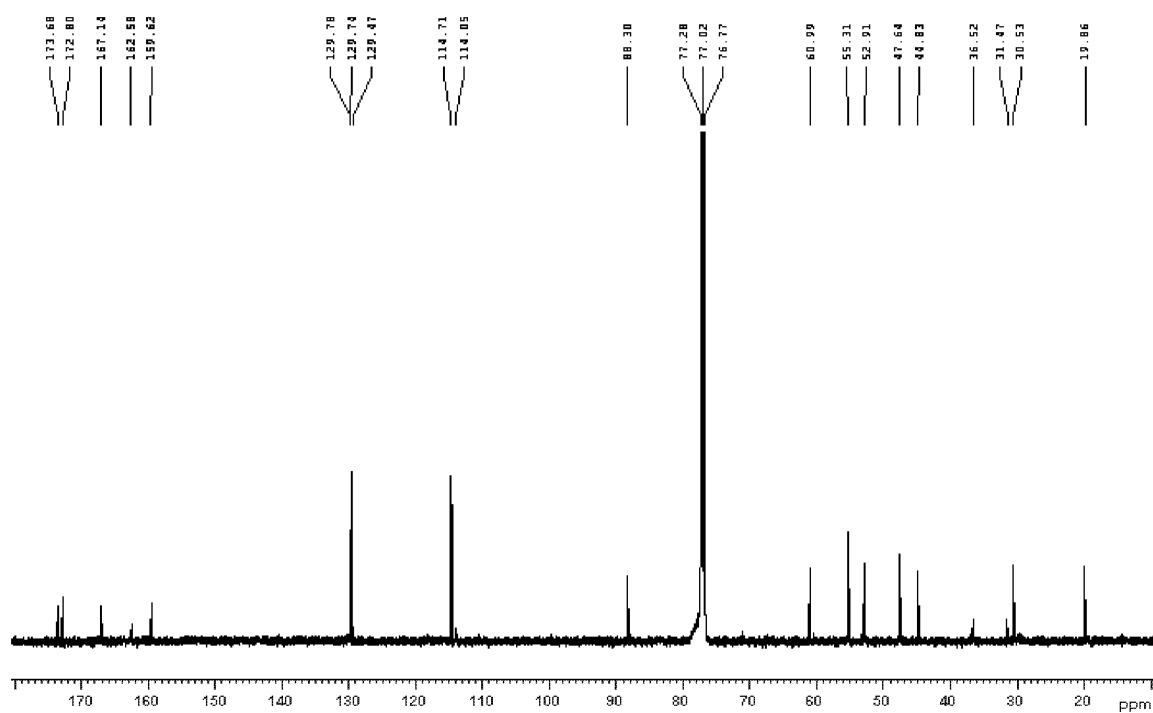


Fig. 48: ^1H NMR spectrum of Compound (XI-2A) ($\text{R}^2 = \text{methyl}$ and C-5-O-TES) in CDCl_3 .

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Fig. 49: ¹H NMR spectrum of Compound (XII-2A) (R^2 = methyl) in $CDCl_3$.Fig. 50: ¹³C NMR spectrum of Compound (XII-2A) (R^2 = methyl) in $CDCl_3$.

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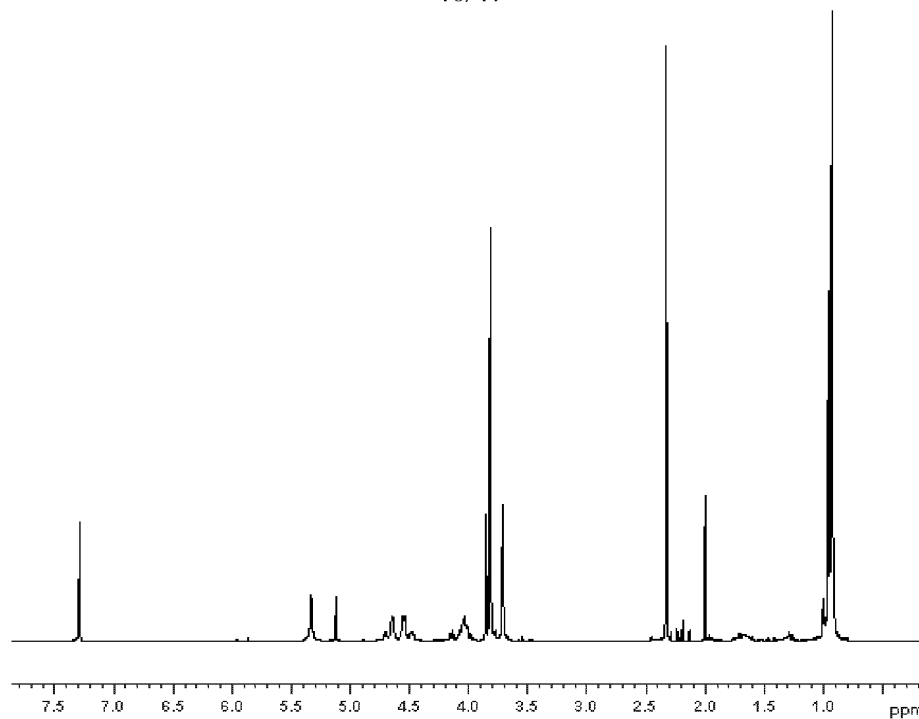


Fig. 51: ¹H NMR spectrum of the compound of formula (III-2A) (R^1 = t-butyl and R^2 = methyl) in CDCl₃.

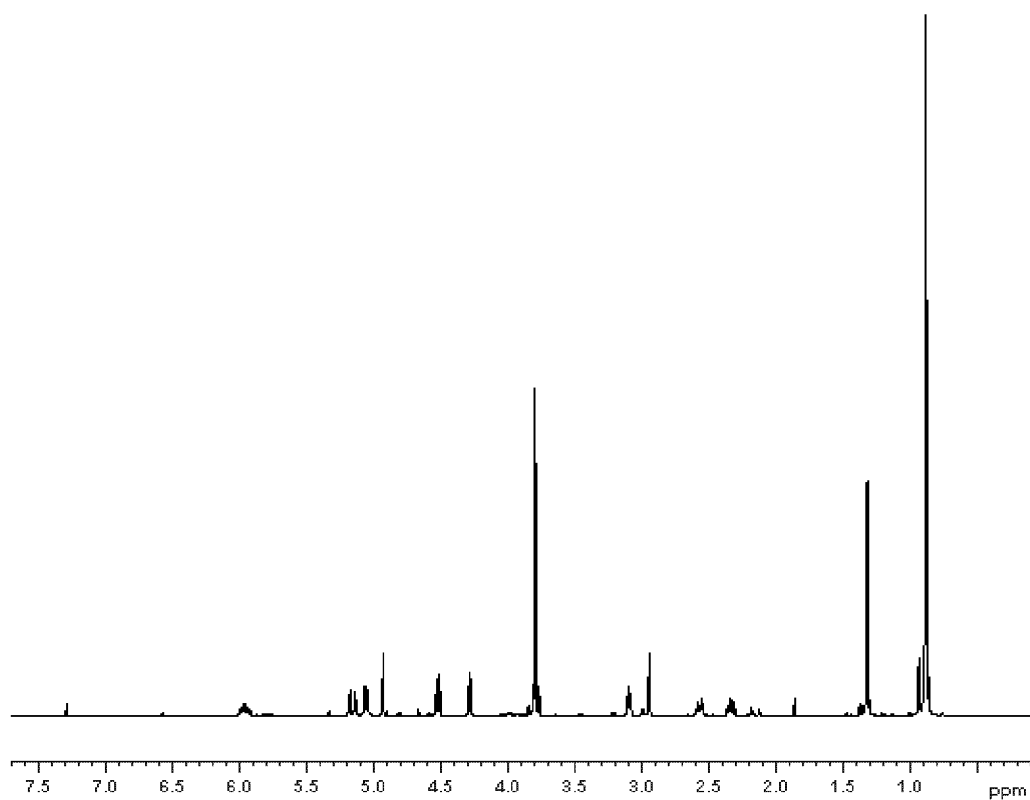


Fig. 52: ¹H NMR spectrum of the compound of formula (Va-A) (R^1 = t-butyl and R^2 = methyl) in CDCl₃.

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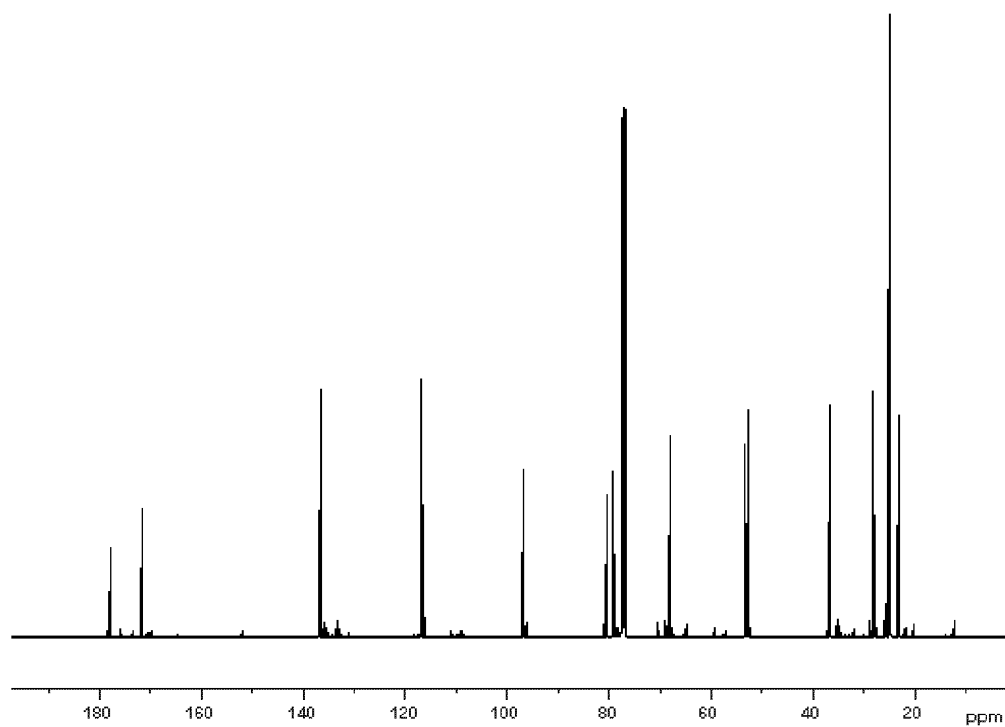


Fig. 53: ^{13}C NMR spectrum of the compound of formula (Va-A) ($\text{R}^1 = \text{t-butyl}$ and $\text{R}^2 = \text{methyl}$) in CDCl_3 .